EXAMINING MEDICAL PRODUCT DEVELOPMENT IN THE WAKE OF THE EBOLA EPIDEMIC

HEARING

BEFORE THE

SUBCOMMITTEE ON HEALTH

OF THE

COMMITTEE ON ENERGY AND COMMERCE

HOUSE OF REPRESENTATIVES

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C O N T E N T S

WITNESSES

SUBMITTED MATERIAL

[1] Ms. Borio did not answer submitted questions for the record by the time of printing.

EXAMINING MEDICAL PRODUCT DEVELOPMENT IN THE WAKE OF THE EBOLA EPIDEMIC

WEDNESDAY, NOVEMBER 19, 2014

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON HEALTH,
COMMITTEE ON ENERGY AND COMMERCE,
Washington, DC.

The subcommittee met, pursuant to call, at 10:35 a.m., in room 2123, Rayburn House Office Building, Hon. Joseph R. Pitts (chairman of the subcommittee) presiding.

Members present: Representatives Pitts, Burgess, Murphy, Blackburn, McMorris Rodgers, Lance, Cassidy, Guthrie, Griffith, Bilirakis, Ellmers, Barton, Capps, Green, Barrow, Castor, and Waxman.

Staff present: Clay Alspach, Chief Counsel, Health; Brenda Destro, Professional Staff Member, Health; Brad Grantz, Policy Coordinator, Oversight and Investigations; Sydne Harwick, Legislative Clerk; Brittany Havens, Legislative Clerk; Carly McWilliams, Professional Staff Member, Health; Katie Novaria, Professional Staff Member, Health; Alan Slobodin, Deputy Chief Counsel, Oversight; Heidi Stirrup, Health Policy Coordinator; Tom Wilbur, Digital Media Advisor; Ziky Ababiya, Democratic Staff Assistant; Eric Flamm, Democratic FDA Detailee; Hannah Green, Democratic Policy Analyst; Amy Hall, Democratic Senior Professional Staff Member; Karen Nelson, Democratic Deputy Committee Staff Director for Health; and Rachel Sher, Democratic Senior Counsel.

Mr. PITTS. The subcommittee will come to order. The Chair will recognize himself for an opening statement.

OPENING STATEMENT OF HON. JOSEPH R. PITTS, A REPRESENTATIVE IN CONGRESS FROM THE COMMONWEALTH OF PENNSYLVANIA

The world is currently experiencing the largest Ebola outbreak in history. The worldwide death toll is at least 5,177 people, according to the World Health Organization's November 14 situation report. Although the initial response to the Ebola outbreak was slow, it is now a top priority for the global public health community, including the United States.

At today's hearing, the subcommittee will examine an important aspect of the Ebola crisis, medical product development. As Ebola spreads, therapeutics are desperately needed to prevent, diagnose, and treat the disease. Federal agencies and drug and device manu-

facturers are hurrying to find treatments, vaccines, and diagnostics for this deadly disease. Adding to the frustration, none of the medications with the most promise are FDA-approved and therefore must be tested in clinical trials, which will take time.

In light of the Nation's substantial investment in public health emergency preparedness, many are wondering why no proven Ebola medications are currently available and what the Federal Government is doing to expedite their approval: Specifically, what is FDA doing to accelerate their review of products? How is BARDA assisting companies to prepare for clinical trials? What is the plan for manufacturing? And how and where will these medical products be distributed once they are approved or cleared?

Questions are also being asked about the administration's recent $6.18 billion emergency appropriations request, including how much of the request is for development of medical products and how previous funding requests have been allocated and spent. I would like to thank all of our witnesses for being here today. I look forward to hearing your testimony.

[The prepared statement of Mr. Pitts follows:]

PREPARED STATEMENT OF HON. JOSEPH R. PITTS

The world is currently experiencing the largest Ebola outbreak in history. The worldwide death toll is at least 5,177 people, according to the World Health Organization's November 14th situation report.

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In light of the Nation's substantial investment in public health emergency preparedness, many are wondering why no proven Ebola medications are currently available and what the Federal Government is doing to expedite their approval.

Specifically, what is FDA doing to accelerate their review of products, how is BARDA assisting companies to prepare for clinical trials, what is the plan for manufacturing, and how and where will these medical products be distributed once they are approved or cleared?

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I would like to thank all of our witnesses for being here today, and I look forward to their testimony.

Mr. PITTS.And I will yield the remainder of my time to our vice chair, Dr. Burgess.

OPENING STATEMENT OF HON. MICHAEL C. BURGESS, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF TEXAS

Mr. BURGESS. Thank you, Mr. Chairman. And thank you for holding this hearing.

Thank you to our witnesses for agreeing to testify with us today. This is now number whatever of a series of hearings on the Ebola outbreak that this committee and other committees have conducted. As I mentioned yesterday in our Oversight and Investigations Subcommittee hearing, one of the things that I think has be-

come abundantly clear in dealing with this crisis is that all of us ought to bear a lot of humility because this virus is different from things we have seen in the past and doesn't always behave the way we expect it to, but this hearing today is not about looking at the past. It is looking at the future and looking toward additional lines of defense, vaccines and therapeutics and diagnostics to aid in the fight of this epidemic.

I can remember in medical school when I read that smallpox was over, that the last cases had been eradicated, and we would never have to deal with the illness again. And the way it was over was by a combination of epidemiologic studies and isolation, but also vaccination, so anyone who was exposed to the illness, the ring around them, the ring vaccination approach, was used so that any contacts were not just identified, but they were also vaccinated. And that did prove extremely effective in halting the progress of what at that time was a very terrible disease. And it wasn't in fact until I was elected to Congress that I realized that smallpox was in fact not eradicated, and we still had to be concerned about it.

But the point is that development of a vaccine will significantly aid in the fight against this illness. And for our aid workers and for our soldiers going to Western Africa to be on the front lines, we really do owe them the development of a vaccine so that they can feel protected as they, in fact, go forward to do good for their fellow humans.

I can't underscore the significance of people who are coming back who certainly want to know not only are they protected while they are away, but they are not bringing something back to their families, and particularly important I know to the men and women in the Armed Forces who are serving in Western Africa currently trying to help stem the flow of the epidemic.

I hope to hear this morning about the FDA utilizing a commonsense risk profile when evaluating diagnostics and vaccinations. On my visits down to Presbyterian Hospital the last couple of weeks, certainly I learned that the FDA was accommodating with hearing requests from people who were on the front lines of treating patients. For that, I am grateful. And I would like to hear what, going forward, what we can look to as far as help from the regulatory side.

Thank you, Mr. Chairman, for having the hearing, and I will yield back.

Mr. PITTS. The Chair thanks the gentleman.

Now recognize the ranking member of the full committee, Mr. Waxman, 5 minutes for an opening statement.

OPENING STATEMENT OF HON. HENRY A. WAXMAN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF CALIFORNIA

Mr. WAXMAN. Thank you very much, Mr. Chairman.

The Ebola epidemic in West Africa is a devastating public health crisis. To date, more than 5,000 people have died from the disease and over 14,000 people have been infected, according to the Centers for Disease Control and Prevention. Many more cases are expected as this crisis overwhelms the affected countries' public health systems.

We have a responsibility to help end this outbreak, not only to help alleviate the suffering of those in West Africa but also to prevent this devastating illness from spreading further. And we must take actions now to prevent outbreaks like this from occurring again in the future.

Today's hearing will focus on one important piece of this goal, drug and vaccine development for treatment and prevention of Ebola. We need to look closely at why there are essentially no effective medicines or vaccines for this devastating illness.

In the United States, we rely on the pharmaceutical industry to discover, develop, and deliver new medicines to patients. This system works because there is a sufficient patient population that needs new medicines, our healthcare system can pay for the new treatments, and the industry can thereby recoup its investment. But Ebola is different. The need for the drug is sporadic. The U.S. patient population is almost nonexistent. And the countries with the most Ebola patients cannot afford to pay high prices.

So this is an instance in which the private market does not work. With Ebola, the Federal Government must drive the development of medicines by working with pharmaceutical companies. At our last hearing, we heard that the Federal agencies have indeed stepped up their efforts. The committee has also heard from companies with promising drug diagnostic or vaccine candidates who told us that the Government has been acting as an effective partner. For our Federal agencies to continue to support the development of these products, Congress must provide increased funding now and ensure the stability of that funding going forward. That is why I support President Obama's emergency request. The request would provide the resources needed immediately to strengthen the ability of U.S. public health systems to respond to Ebola and address the current outbreak in West Africa. It includes over $400 million for NIH, FDA, and BARDA, the Biomedical Advanced Research and Development Authority, to support the development, manufacture, and testing of Ebola diagnostics, therapeutics, and vaccines, and the request also sets the groundwork to strengthen global health systems to better prevent, detect, and respond to future disease outbreaks. Congress must act on this request promptly, but we also need to make sure that this isn't a one-time funding increase in the wake of an emergency. We should avoid a cycle in which we let our guard down once the immediate public health crisis passes and don't renew our efforts until the next emergency occurs and we find ourselves unprepared again. This kind of boom-bust approach to preparedness simply does not work. We must ensure that we establish a continuous operation and provide continuous funding so we are prepared for the next outbreak. I thank the witnesses for being here today and for your tireless efforts to help alleviate the suffering of those afflicted by the Ebola outbreak in West Africa.

Mr. Chairman, we need to do everything we can. At the minimum, we need to support the President's request so we can have this country do what is necessary in Africa and here at home to address this crisis. Yield back my time.

[The prepared statement of Mr. Waxman follows:]

PREPARED STATEMENT OF HON. HENRY A. WAXMAN

The Ebola epidemic in West Africa is a devastating public health crisis. To date, more than 5,000 people have died from the disease and over 14,000 people have been infected, according to the Centers for Disease Control and Prevention. Many more cases are expected as this crisis overwhelms the affected countries' public health systems.

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But we also need to make sure this isn't a one-time funding increase in the wake of an emergency. We should avoid a cycle in which we let our guard down once the immediate public health crisis passes and don't renew our efforts until the next emergency occurs, and we find ourselves unprepared again. This kind of "boom/bust" approach to preparedness simply does not work. We must ensure that we establish a continuous operation—and provide continuous funding—so we are prepared for the next outbreak.

I thank the witnesses for being here today and for your tireless efforts to help alleviate the suffering of those afflicted by the Ebola outbreak in West Africa.

Mr. PITTS. The Chair thanks the gentleman.

I now recognize the vice chair of the full committee, Mrs. Blackburn, 5 minutes for an opening statement.

OPENING STATEMENT OF HON. MARSHA BLACKBURN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF TENNESSEE

Mrs. BLACKBURN. Thank you, Mr. Chairman.

We now have about 15,000 cases and over 5,000 deaths in this 2014 Ebola outbreak. It is the worst since the virus was discovered in 1976, and we are hearing some good news out of Liberia, some mixed results out of the region. And in light of this outbreak, there should be an intensive effort to find and approve a treatment or, better yet, a vaccine to prevent Ebola. And Dr. Burgess has spoken so well about that and our concerns.

Now, the FDA and the FDA Priority Review Voucher Program was authorized by Congress in 2007 to incentivize the development for neglected tropical diseases. And although Congress did provide FDA with the ability to add diseases to this list through rulemaking, the process still takes time. That is why I have introduced H.R. 5729, which would add the filoviruses to the list of diseases included in the Priority Review Voucher Program. This family includes all known strains of Ebola as well as the related Marburg viruses.

And I want to recognize and thank my cosponsors on this bipartisan legislation: Representatives Green, Butterfield, McCaul, and Fleischmann. I also ask for the support of the rest of the committee members. This is an issue that needs and deserves our attention. And we stand ready to work with you. We welcome you as our witnesses today.

And Mr. Chairman, I would yield the remaining time to whomever would like it.

Mr. PITTS. Does anyone seek time?

Mrs. BLACKBURN. I yield back.

Mr. PITTS. The Chair thanks the gentlelady.

That concludes our opening statements. Members' opening written statements will be made a part of the record.

We have one panel today. On our panel, we have today Dr. Anthony Fauci, Director of the National Institute of Allergy and Infectious Diseases of the National Institutes of Health; Dr. Luciana Borio, Director, Office of Counterterrorism and Emerging Threats, U.S. Food and Drug Administration; Rear Admiral Stephen Redd, senior adviser for Ebola response, Centers for Disease Control and Prevention; and Dr. Robin Robinson, Director, Biomedical Advanced Research and Development Authority at the Office of the Assistant Secretary for Preparedness and Response, U.S. Department of Health and Human Services.

Thank you for coming. Your written testimony will be made a part of the record. You will have each 5 minutes to summarize your testimony, and we will begin with you, Dr. Fauci. you are recognized for 5 minutes for your opening statement.

STATEMENTS OF ANTHONY S. FAUCI, DIRECTOR, NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASE, NATIONAL INSTITUTES OF HEALTH, DEPARTMENT OF HEALTH AND HUMAN SERVICES; LUCIANA BORIO, DIRECTOR, OFFICE OF COUNTERTERRORISM AND EMERGING THREATS, FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES; STEPHEN C. REDD, SENIOR ADVISOR FOR EBOLA RESPONSE, CENTERS FOR DISEASE CONTROL AND PREVENTION; ROBIN A. ROBINSON, DIRECTOR, BIOMEDICAL ADVANCED RESEARCH AND DEVELOPMENT AUTHORITY, OFFICE OF THE ASSISTANT SECRETARY FOR PREPAREDNESS AND RESPONSE, DEPARTMENT OF HEALTH AND HUMAN SERVICES

STATEMENT OF ANTHONY S. FAUCI

Mr. FAUCI. Thank you very much, Chairman Pitts, Vice Chairman Burgess, Ranking Member Waxman.

I appreciate the opportunity to address you today on the role of the National Institute of Allergy and Infectious Diseases in the research which is addressing our response to the Ebola virus disease epidemic. This particular effort—interestingly, not fully appreciated—actually began many years ago following the attacks on 9/11 at the World Trade Center and at the Pentagon, which the following month were followed by anthrax attacks through letters to the United States Congress and the press, which triggered a multiagency Government effort to address the medical countermeasures for bioterror. And as shown on this slide, there was a research agenda in which a variety of pathogens were identified to be the high-risk pathogens for bioterror attacks. And if you look on the bottom of the slide, there is anthrax, botulism, plague, smallpox, tularemia, but the viral hemorrhagic fevers are listed prominently there, including Ebola.

Years ago, we made the decision that not only would we need to be prepared for deliberate attacks in the form of bioterror but for the natural emergence and reemergence of these infectious diseases, so the biodefense agenda was merged into an agenda for naturally emerging and reemerging infections, and so the NIH put on a multifaceted effort that ranged from fundamental basic research through clinical research and the provision of resources for academic investigators and industries, with the result in mind of ultimately developing countermeasures in the form of diagnostics, therapeutics, and vaccines. And, as represented on this committee, what we had was a variety of agencies synergizing with each other. The NIH doing the concept and early product development, advanced development on the part of BARDA, which you will hear from Dr. Robinson soon, the commercial manufacturing, and finally the regulatory guidance and review by the FDA. Using this framework, we have products now that are in the various stages of the process of development.

I bring to your attention two that are most important, and that is Ebola vaccines in which we started the early phase I trials at the NIH on September the 2nd. We have completed enrollment and vaccinations. We have the early results of the product of the GSK Vaccine Research Center showing minimum adverse events and good immunogenicity. Soon behind that is the VSV or NewLink product, which entered phase I trials soon after the September initiation of trials at the NIH. And they are both now being studied at the NIH and by the Walter Reed Army Medical Center. There are a couple of others behind them, and we hope to begin Phase II/III trials for efficacy in West Africa by the very early part of next year, likely the first week or so in January. My deputy is currently in Liberia now determining the logistics of the trial.

In addition, there are therapeutics that are in development. Here is a list of some of them. I don't have time to go through all of them. But each of these in one form or another has been given on a compassionate basis to individuals who have been stricken with Ebola virus disease.

The one point I want to make to this committee is that we do not know if any of them work or how toxic any of them are, which really cries out for the kinds of clinical trials which we are cur-

rently designing to determine in a definitive manner the safety and efficacy of these products.

I would like to close in the last minute to also bring to the attention of this committee that the NIH also has a Special Clinical Studies Unit at our Clinical Center in Bethesda. And we are designated, as shown on the map, as one of the three designated Ebola treatment facilities, along with our colleagues at Emory and at Nebraska. On the lower right is a picture of the Clinical Center, and you won't recognize me, but on the left-hand part of the slide is a picture of me as I was getting ready to go into the room to help take care of Nina Pham, who was a patient at the Clinical Center. And I am happy to say I think we already know that, as shown on this last slide, we were very happy and fortunate to have the opportunity to discharge her a couple of weeks ago. There is a picture of her on the left, and on the right is a picture of the nurses who helped us take care of her.

That is the end of my testimony, Mr. Chairman. I will be happy to answer questions later on.

[The prepared statement of Mr. Fauci follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

The Role of the National Institute of Allergy and Infectious Diseases Research in Addressing Ebola Virus Disease

Testimony before the

House Committee on Energy and Commerce

Subcommittee on Health

Anthony S. Fauci, M.D.

Director

National Institute of Allergy and Infectious Diseases

November 19, 2014

Mr. Chairman, Ranking Member Pallone, and Members of the Subcommittee:

Thank you for the opportunity to discuss the National Institutes of Health (NIH) response to the global health emergency of Ebola virus disease. I direct the National Institute of Allergy and Infectious Diseases (NIAID), the lead institute of the NIH for conducting and supporting research on infectious diseases, including viral hemorrhagic fevers such as those caused by Ebola virus infection.

For more than six decades, NIAID has made important contributions to advancing the understanding of infectious, immunologic, and allergic diseases, from basic research on mechanisms of disease to applied research to develop diagnostics, therapeutics, and vaccines. NIAID has a dual mandate that balances research addressing current biomedical challenges with the capacity to respond quickly to newly emerging and re-emerging infectious diseases, including bioterror threats. Critical to these efforts are NIAID's partnerships with academia, pharmaceutical companies, international organizations such as the World Health Organization (WHO), and collaborations with other Federal entities, particularly the Centers for Disease Control and Prevention, the Food and Drug Administration (FDA), the Office of the Assistant Secretary for Preparedness and Response, including the Biomedical Advanced Research and Development Authority (BARDA), and the Department of Defense (DOD).

OVERVIEW OF EBOLA VIRUS DISEASE

Viral hemorrhagic fevers are severe illnesses that can be fatal and are caused by a diverse group of viruses including Marburg virus, Lassa virus, and Ebola virus. Infection with Ebola virus typically causes fever, severe vomiting and diarrhea resulting in profound fluid loss, rash, weakness, electrolyte loss, impaired kidney and liver function, and in some cases internal and

external bleeding. Since the discovery of Ebola virus in 1976, outbreaks of hemorrhagic fever caused by Ebola virus have had fatality rates ranging from 25 percent to 90 percent, depending on the species of virus and the availability of medical facilities and staff to care for infected patients. West Africa is currently experiencing the most severe Ebola outbreak ever recorded. As of November 11, 2014, there have been 14,413 reported cases, including 5,177 documented deaths according to the WHO. The ongoing Ebola epidemic in Guinea, Liberia, and Sierra Leone has generated far more cases and deaths than the 24 previous Ebola outbreaks combined. The recent death of a patient diagnosed with Ebola in Dallas, Texas, after traveling from Liberia, and the cases transmitted outside of Africa (to two healthcare workers in Dallas and a nurse in Spain) intensify our concerns about this global health threat.

The ongoing public health crisis in West Africa demands a major amplification of efforts to identify and isolate infected individuals, perform contact tracing, and provide personal protective equipment for healthcare workers involved in the treatment of infected individuals. This still remains the time-proven approach to controlling and ultimately ending the epidemic. However, there is also a critical need to develop improved diagnostics, as well as safe and effective therapeutics and vaccines for Ebola. Although fluid replacement and attention to electrolyte balance can greatly increase survival, there are no Ebola-specific FDA-approved interventions available at this time. In this regard, NIAID has a longstanding commitment to advancing research to combat Ebola while ensuring the safety and efficacy of potential medical countermeasures such as treatments and vaccines.

HISTORY OF NIAID EBOLA VIRUS RESEARCH: RELATIONSHIP TO BIODEFENSE RESEARCH

The ability to safely and effectively prevent and treat Ebola virus infection is a longstanding NIAID priority. Since the 2001 anthrax attacks, NIAID has vastly expanded its research portfolio in biodefense and naturally emerging and re-emerging infectious diseases. This research targets pathogens that pose high risks to public health and national security. NIAID has designated pathogens with high mortality such as anthrax, plague, smallpox, and Ebola virus as NIAID Category A Priority Pathogens to highlight the need for medical countermeasures against these dangerous microbes.

NIAID's expanded research efforts in biodefense and emerging and re-emerging infectious diseases focus on specific objectives. The first is to advance basic and translational research and facilitate development of effective products to combat deadly diseases such as Ebola. The second is to employ innovative strategies, such as broad spectrum vaccines and therapeutics, to prevent and treat a variety of related infectious diseases. The third is to strengthen our partnerships with biotechnology and pharmaceutical companies to help accelerate the availability of needed products for affected and at-risk individuals.

Since 2001, NIAID's biodefense research has supported the development and testing of numerous candidate products to prevent or treat viral hemorrhagic fevers, including those caused by Ebola and other related viruses. The progress we have made with candidate vaccines, therapeutics, and diagnostics for Ebola virus would not be possible had we not made this important investment.

DEVELOPMENT AND TESTING OF EBOLA MEDICAL COUNTERMEASURES

In response to the Ebola public health emergency in West Africa, NIAID is accelerating ongoing research efforts and partnering with governments and private companies throughout the world to speed the development of medical countermeasures that could help control the current epidemic and future outbreaks. NIAID research on Ebola virus focuses on basic research to understand how Ebola virus causes illness in animals and in people, as well as pathogen evolution and transmission, and viral ecology. Advances in these areas are complemented by translational research developing diagnostics, vaccines, and therapeutics.

Diagnostics

Accurate and accessible diagnostics for Ebola virus infection are needed for the rapid identification and treatment of patients in an outbreak because the symptoms of Ebola can be easily mistaken for other common causes of fever in affected areas, such as malaria. NIAID continues to provide resources to investigators attempting to develop Ebola diagnostics. With NIAID support, Corgenix Medical Corporation is developing rapid immunodiagnostics for Ebola viruses using genomic technology to produce recombinant viral proteins. NIAID also is advancing development of other types of diagnostics, including those using novel technologies such as microfluidics, optofluidics and nanophotonics, which are capable of detecting an array of viruses including Ebola. Such innovative approaches can provide information critical to the creation of rapid point-of-care diagnostics that could be distributed and used in areas where Ebola virus outbreaks occur. Intramural scientists from NIAID's Rocky Mountain Laboratories (RML) in Hamilton, Montana, and the Integrated Research Facility in Frederick, Maryland, have responded to the epidemic by establishing and staffing diagnostic laboratory field sites in

Monrovia, Liberia, in coordination with CDC, to identify the presence or absence of Ebola virus in clinical samples. These real-time data are critical to patient care and monitoring of the epidemic. NIAID and CDC researchers also have established collaborations with Malian public health institutes, providing training in laboratory testing for identification of Ebola and other fever-causing viruses.

Therapeutics

Currently, supportive care, including careful attention to fluid and electrolyte replacement, is the only effective medical intervention for patients with Ebola virus disease; no drugs are available that have been shown safe and effective specifically to treat Ebola virus infection. Experts are now evaluating whether drugs licensed or approved for the treatment of other diseases should be reevaluated for potential treatment of patients with Ebola in the current epidemic on an emergency basis. In parallel, NIAID is supporting the development of novel therapeutics targeting Ebola virus. These investigational candidate therapeutics could possibly be used in clinical trials in the current epidemic and hopefully will prove to be safe and effective; if so, such treatments could be more widely available for future outbreaks. It is important to note that NIAID-supported candidate therapeutics are in early development and are currently available only in limited quantities.

NIAID has provided support to and collaborated with Mapp Biopharmaceutical, Inc., to develop MB-003, a combination of three antibodies that prevents Ebola virus disease in monkeys when administered as late as 48 hours after exposure. An optimized product derived from MB-003, known as ZMapp, has shown to be substantially more effective in animal models than earlier combinations and protected monkeys from death due to Ebola virus up to five days after infection, according to Mapp Biopharmaceutical, Inc. NIAID's preclinical services are now

being used to provide pivotal safety data to support the use of ZMapp for clinical trials in humans. Mapp Biopharmaceutical, Inc., has announced that ZMapp was recently administered to humans for the first time as an experimental treatment to several Ebola-infected patients, including two Americans. It is not possible at this time to determine whether ZMapp benefited these patients. NIAID is working closely with partners at DOD, BARDA, and FDA to advance development and testing of ZMapp to determine whether it is safe and effective. BARDA has recently announced plans to optimize and accelerate the manufacturing of ZMapp so that clinical safety testing can proceed as soon as possible.

NIAID also has funded BioCryst Pharmaceuticals to develop and test BCX4430, a novel drug that interferes with the reproductive process of the virus and has activity against a broad spectrum of viruses. According to BioCryst, BCX4430 has protected animals against infection with Ebola virus and the related Marburg virus. BioCryst has announced that a Phase 1 clinical trial of this drug is expected to begin in late 2014 or early 2015. NIAID also is evaluating therapeutics licensed or in development for the treatment of other diseases for their potential activity against Ebola virus. One of these investigational agents is brincidofovir, an antiviral originally developed with NIAID support for use against other viruses.

Vaccines

A safe and effective Ebola vaccine could be a critically important tool to help prevent Ebola virus disease and help contain future outbreaks. The hope is that such a vaccine could be licensed and used in the field to protect frontline healthcare workers and individuals living in areas where Ebola virus exists. Two Ebola vaccine candidates are undergoing Phase 1 clinical testing this fall. NIAID will play a critical role in advancing these Ebola vaccine candidates. The

results of these Phase 1 studies will inform essential discussions about whether and how such vaccines could be of use in the current epidemic or future Ebola outbreaks.

The NIAID Vaccine Research Center (VRC) has a robust viral hemorrhagic fever vaccine development program. Since 2003, the VRC has evaluated three early-generation Ebola vaccine candidates and one Marburg vaccine candidate in Phase 1 clinical trials at the NIH campus. An additional Phase 1 clinical trial was conducted in Kampala, Uganda, in collaboration with DOD. None of the early-generation candidates raised safety concerns in these small trials; however, they did not elicit the level of immune response thought to be needed to provide protection against the viruses. The data from those trials have contributed directly to the VRC's current Ebola vaccine collaboration with the pharmaceutical company GlaxoSmithKline (GSK). VRC and GSK have developed an experimental vaccine that uses a chimpanzee virus (similar to the common cold virus), Chimp Adenovirus 3 (CAd3), as a carrier, or vector, to introduce Ebola virus genes into the body; these genes encode Ebola proteins that stimulate an immune response. The vaccine candidate has shown promising results in animal models against two Ebola virus species (bivalent vaccine), including the Zaire Ebola species responsible for the current epidemic in West Africa. A small Phase 1 study to examine the safety and ability of this candidate to induce an immune response in humans began on September 2, 2014, at the NIH Clinical Center in Bethesda, Maryland. All twenty of the study volunteers have been vaccinated. The trial has now moved forward to two other U.S. sites (University of Maryland and Emory University) to gather additional safety and immunogenicity data. Results from all sites are anticipated by the end of 2014 and will inform future development of the vaccine.

As part of the Phase 1 studies, the NIH is also supporting testing of a related vaccine candidate, including just a single Ebola virus gene from the Zaire Ebola virus (monovalent

vaccine). NIAID and GSK also have donated doses of this vaccine candidate to enable further testing by NIAID partners in the United Kingdom and the West African country of Mali. In October, GSK and WHO partners began an additional, larger clinical study of the monovalent vaccine in Geneva/Lausanne, Switzerland.

Additionally, NIH is collaborating with DOD and NewLink Genetics Corporation on Phase 1 safety studies of an investigational Ebola vaccine based on the vesicular stomatitis virus (VSV). The VSV will serve as a vector or carrier for an Ebola gene similar to how the Chimp adenovirus serves as a vector or carrier as described above for the NIAID/GSK vaccine. This vaccine candidate was developed by and licensed from the Public Health Agency of Canada.

In addition to these Ebola candidates entering Phase 1 trials in 2014, NIAID supports a broad portfolio of Ebola vaccine research. NIAID has supported the biopharmaceutical company Crucell to develop a recombinant adenovirus-vectored Ebola vaccine. In animal studies, this vaccine candidate protected against filovirus infection, including Ebola virus. NIAID has played an instrumental role in the recently announced collaboration between Johnson & Johnson (parent company of Crucell) and Bavarian Nordic. Crucell will contribute its adenovirus-vectored vaccine and Bavarian Nordic will contribute its modified vaccinia virus Ankara (MVA)-vectored vaccine for a two-dose (prime-boost) vaccination regimen that will begin Phase 1 testing in early 2015.

NIAID intramural scientists are collaborating with Thomas Jefferson University investigators to produce a vaccine candidate based on an existing rabies vaccine. The researchers aim to generate immunity to Ebola, Marburg, and rabies viruses, important diseases in certain regions in Africa. The investigators plan to pursue a version of the vaccine for human and veterinary use, as well as a version for use in African wildlife. The wildlife vaccine could help

prevent transmission of Ebola virus from animals to humans. The vaccine candidate for use in humans is undergoing preclinical testing and has demonstrated protection against infection by rabies and Ebola viruses in animal models. NIAID is currently partnering with DOD to produce sufficient quantities of the vaccine candidate to begin clinical testing in 2015. In September, NIH licensed the candidate rabies/Ebola vaccines to Exxell BIO of St. Paul, Minnesota, which aims to advance the products through clinical testing and potential commercialization.

NIAID also is supporting the biotechnology company Profectus BioSciences, Inc., to investigate a second recombinant VSV-vectored vaccine candidate against Ebola and Marburg viruses. Profectus is pursuing preclinical testing of the vaccine in preparation for a future Phase 1 clinical trial. Additionally, NIAID is collaborating with the Galveston National Laboratory & Institute for Human Infections and Immunity at the University of Texas Medical Branch at Galveston to advance progress made by NIAID intramural scientists on a paramyxovirus-based vaccine against Ebola virus. Production of the paramyxovirus-based vaccine is in progress to enable clinical testing planned for mid-2015.

Other NIAID-supported efforts include Ebola virus vaccine candidates in early development, such as a DNA vaccine targeting Ebola and Marburg viruses, an adenovirus-5-based intranasal Ebola vaccine, and a combination virus-like particle/DNA vaccine targeting Ebola and Marburg viruses to be delivered by microneedle patch. Knowledge gained through these studies will further the goal of the ultimate deployment of a safe and effective vaccine that will prevent this deadly disease.

NIAID also advances vaccine product development by providing preclinical services such as animal testing to researchers in academia and industry. More than 30 different filovirus vaccine formulations have been evaluated through NIAID's preclinical services since 2011 using

animal models and assays that NIAID has developed over many years. Several of these candidates qualified for further testing and a number are currently in the product development pipeline.

Clinical Trials to Evaluate Efficacy

It is important to balance the urgency to deploy investigational medical countermeasures in an emergency such as the current Ebola outbreak with the need to ensure the maximal safety and to determine the efficacy of candidate drugs and vaccines for Ebola. We will do this with the strictest attention to safety considerations, established scientific principles, and ethical considerations, and compassion for and realization of the immediate needs of the affected populations. The United States Government, working in partnership with industry, has an established mechanism for testing and reviewing the safety and efficacy of potential medical interventions. Randomized controlled clinical trials remain the "gold standard" for the evaluation of candidate drugs and vaccines because they represent the most efficient way to prove efficacy and lack of an unexpected harmful effect. This is particularly important for vaccines since they are administered to healthy individuals.

NIAID is committed to working with our partners to evaluate candidate drugs and vaccines for safety and efficacy. We are working to generate the evidence to show whether potential interventions are safe and effective to reassure affected communities that we are developing the tools needed to prevent and treat this deadly disease. Our partnerships with industry will be critical to move these products expeditiously along the development pipeline into clinical trials. The data from the current Phase 1 trials will help demonstrate whether these candidate Ebola vaccines are safe in humans and are capable of generating an immune response. Candidate Ebola treatments will be similarly evaluated for safety and markers of potential

efficacy. If successful, these candidates will be advanced to efficacy testing in larger numbers of people in West Africa. As we proceed through clinical testing, we will continue to work with our partners in the FDA and BARDA to accelerate development of and speed access to the products, while also protecting the safety and rights of study volunteers.

CONCLUSION

While NIAID is an active participant in the global effort to address the public health emergency occurring in West Africa, it is important to recognize that we are still in the early stages of understanding how infection with the Ebola virus can be treated and prevented. As we continue to expedite research while enforcing high safety and efficacy standards, the implementation of the public health measures already known to contain prior Ebola virus outbreaks and the implementation of treatment strategies such as fluid and electrolyte replacement are essential to preventing additional infections, treating those already infected, protecting health care providers, and ultimately bringing this epidemic to an end. We will continue to work with biopharmaceutical companies and public health agencies throughout the world to develop and distribute medical countermeasures for Ebola virus disease as quickly as possible. NIAID remains committed to fulfilling its dual mandate to balance research on current biomedical challenges with the capability to mobilize a rapid response to newly emerging and re-emerging infectious diseases.

Hearing of the House Committee on Energy and Commerce, Subcommittee on Health

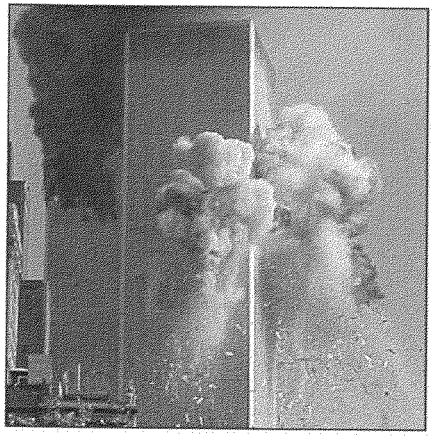
The Role of the National Institute of Allergy and Infectious Diseases in Research Addressing Ebola Virus Disease

Anthony S. Fauci, M.D.
Director
National Institute of Allergy and Infectious Diseases
National Institutes of Health

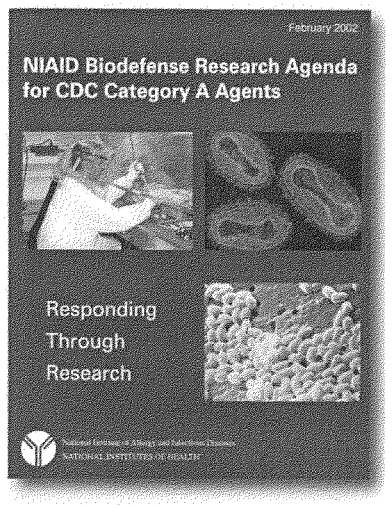
November 19, 2014

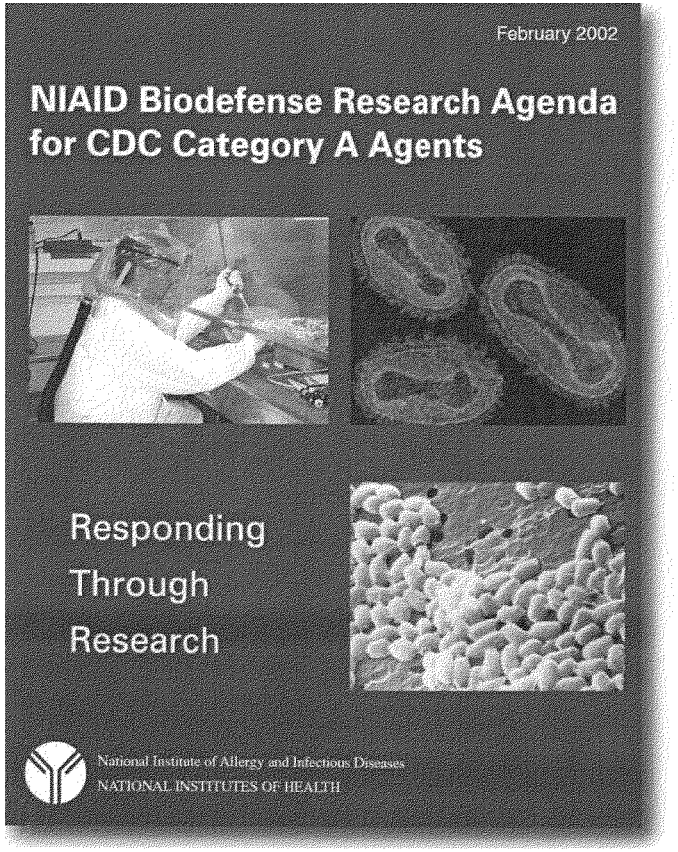
National Institute of Allergy and Infectious Diseases

9/11 Attacks



2001 Anthrax Attacks



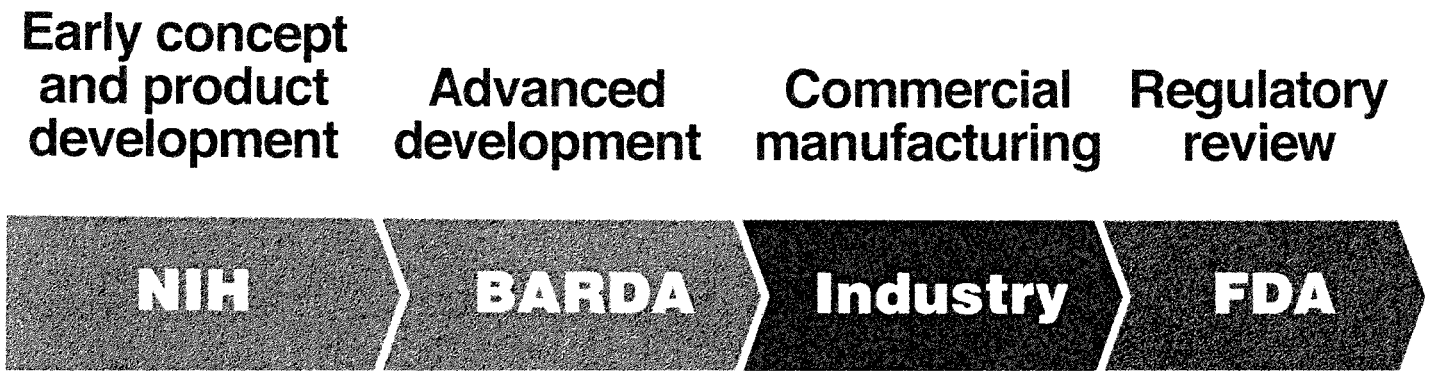


Category A pathogens

- Anthrax (*Bacillus anthracis*)
- Botulism (*Clostridium botulinum* toxin)
- Plague (*Yersinia pestis*)
- Smallpox
- Tularemia (*Francisella tularensis*)
- Viral hemorrhagic fever viruses (e.g., Ebola, Marburg, Lassa and Machupo)

NIH
Countermeasure
Research and
Development
Diagnostics
Therapeutics
Vaccines
Basic Research
Clinical
Research
Resources for
Researchers/
Industry to
Advance
Product
Development

Product Development Pipeline



NIAID Ebola Vaccines Ready to Proceed to Phase 2/3 Efficacy Testing in West Africa

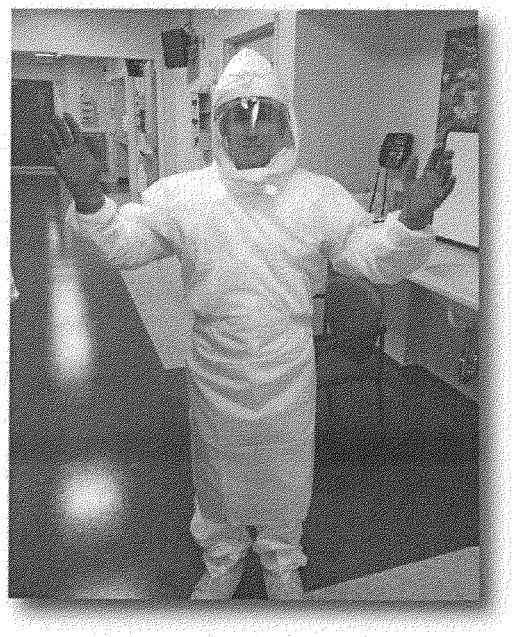
- **NIAID/GSK (chimp adenovirus vector)** — *Phase 1 trial at NIH fully enrolled; Phase 2/3 efficacy trials planned for West Africa*
- **NewLink (VSV vector)** — *Phase 1 trials enrolling at NIH and WRAIR; Phase 2/3 efficacy trials planned for West Africa*

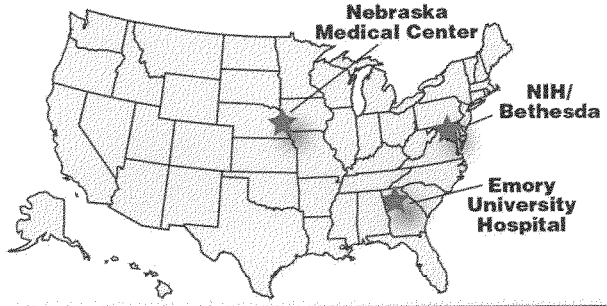
Other vaccines in development: Crucell/Johnson & Johnson (adenovirus vector) and Bavarian Nordic (MVA vector); Profectus (VSV vector); NIAID Intramural, Thomas Jefferson Univ. (rabies vector)

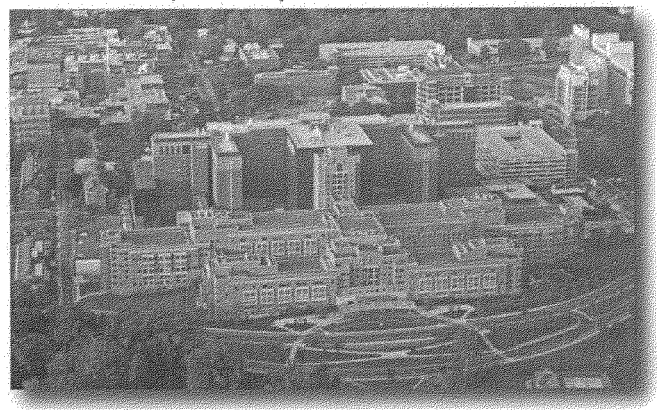
Ebola Therapeutics in Development

- ZMapp (Mapp Biopharmaceutical)
  - Combination of 3 artificially produced antibodies directed against the Ebola virus
- BCX4430 (BioCryst)
  - A novel drug (nucleoside analogue) that interferes with the reproductive process of the virus
- TKM-Ebola (Tekmira Pharmaceuticals)
  - Small inhibitory RNA molecule that interferes with the replication of the virus (supported by DOD)
- Brincidofovir (Chimerix)
  - DNA polymerase inhibitor; *in vitro* activity against Ebola
  - Good safety record; currently in phase 3 trials for CMV and adenovirus
- Favipiravir (MediVector/Toyama/Fuji)
  - Polymerase inhibitor; modest activity against Ebola
  - Currently in phase 3 trials for influenza

NIH Special Clinical Studies Unit: Designated Ebola Treatment Facility







The Washington Post

October 25, 2014

Nina Pham, Nurse Who Contracted Ebola, is Now Free of Virus and Leaves NIH

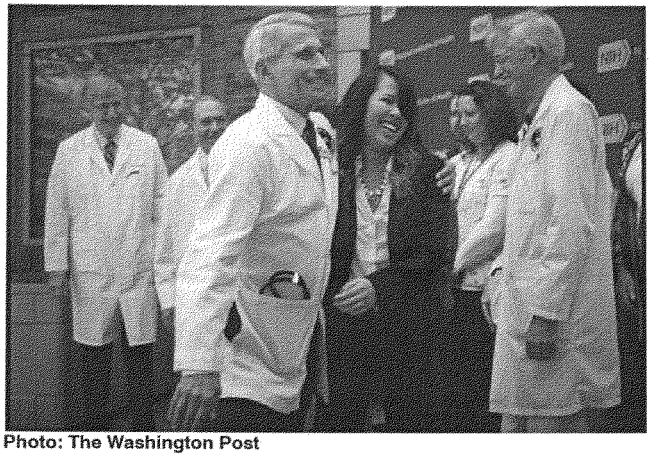


Photo: The Washington Post

Photo: Nina Pham

Mr. PITTS. The Chair thanks the gentleman.

Dr. Borio, you are recognized for 5 minutes for an opening statement.

STATEMENT OF LUCIANA BORIO

Ms. BORIO. Good morning, Chairman Pitts and members of the subcommittee. Thank you for the opportunity to appear before you today to discuss FDA's response to the Ebola epidemic. My colleagues and I are determined to do all we can to help expedite the availability of safe and effective medical products for Ebola. The challenges posed by this epidemic are unprecedented, and the compassion and commitment demonstrated by the healthcare providers caring for patients with Ebola represent the best of humanity.

As you know, currently there are no treatments or vaccines that have been shown to be safe and effective for Ebola. The desire and need for specific treatments and vaccines are overwhelming, and we are taking extraordinary steps to speed the development, manufacture, and availability of these medical products. We are reviewing data as they are received. FDA took only a few days to allow vaccine studies to proceed. We are supporting the World Health Organization by providing technical assistance and advice on scientifically sound, ethical, and efficient clinical trials. We are working with our international regulatory counterparts to achieve regulatory harmonization and efficiencies in the review of investigational products for Ebola, and we are leveraging our authorities. We issued, for example, emergency authorizations for six diagnostic tests for Ebola.

Product development is proceeding at a very accelerated pace, and there is tremendous hope that some of these investigational products will help patients, but as Dr. Fauci just mentioned, these candidates are still in the early stages of development for Ebola. And it is possible that some may hurt patients, and others may have little or no effect. The fastest and most definitive way to assess their safety and efficacy is through properly designed clinical trials.

FDA is working with our NIH colleagues and investigators from the Emory University Hospital, Nebraska Medical Center to implement a flexible and innovative clinical trial protocol that would allow companies and clinicians to evaluate multiple investigational products for Ebola under a common protocol. This will create efficiencies. Our goal is to ensure accrual of interpretable data and generate actionable results in the most expeditious manner. Until such trials are established, we will continue to enable access to investigational products through special mechanisms, such as compassionate use. As you know, every Ebola patient in the U.S. has been treated with at least one investigational product. We have approved such requests for compassionate use within a matter of hours.

But just last week, WHO reviewed the data on the use of investigational products administered to patients under this type of mechanism. They found the data derived did not permit an evaluation of efficacy. This simply underscores the critically important need to establish properly designed and scientifically valid trials to determine whether these products help, hurt or have little or no ef-

fect. What we learn from these trials will have an impact on generations to come.

More than 300 FDA staff are engaged in response activities, and without exception, everyone has been proactive, thoughtful, and adaptive to the complex range of issues that we are facing. There is still a lot of work to do, but we are fully committed to this response. We will continue to leverage our authorities to the fullest extent to facilitate development and availability of safe and effective medical products for Ebola. And our decisions are always based on science, and I can assure you that we will continue to move as fast as the science allows. Thank you very much.

[The prepared statement of Ms. Borio follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

STATEMENT

OF

LUCIANA BORIO, M.D.

ASSISTANT COMMISSIONER FOR COUNTERTERRORISM POLICY

DIRECTOR, OFFICE OF COUNTERTERRORISM AND EMERGING THREATS

DEPUTY CHIEF SCIENTIST (ACTING)

FOOD AND DRUG ADMINISTRATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

SUBCOMMITTEE ON HEALTH

COMMITTEE ON ENERGY AND COMMERCE

U.S. HOUSE OF REPRESENTATIVES

"Examining Medical Product Development in the Wake of the Ebola Epidemic"

November 19, 2014

RELEASE ONLY UPON DELIVERY

INTRODUCTION

Good morning Chairman Pitts, Ranking Member Pallone, and Members of the Subcommittee. I am Dr. Luciana Borio, Assistant Commissioner for Counterterrorism Policy, Director of the Office of Counterterrorism and Emerging Threats, and Acting Deputy Chief Scientist at the Food and Drug Administration (FDA or the Agency). Thank you for the opportunity to appear today to discuss FDA's response to the Ebola epidemic in West Africa—the worst in recorded history.

The toll of this epidemic, with so many lives lost and so many others fighting for their lives, is heartbreaking and tragic. While the outbreaks in Senegal and Nigeria were rapidly contained by the application of standard public health techniques and have now been declared over, disease transmission continues in Guinea, Liberia, and Sierra Leone. In addition, a small cluster of Ebola cases has recently been reported in Mali.

The primary approach to containing the epidemic remains standard public health measures, such as identifying and isolating infected individuals, caring for patients who are ill, ensuring that health care workers have access to personal protective equipment and are properly trained in infection control measures, and tracing patients' contacts to detect any secondary infections, as soon as possible. However, applying these public health measures on a large scale presents complex challenges because of the strains on health care and public health infrastructure within affected countries and the very limited capacity to provide supportive medical care in-country. This tragic situation is further complicated because there are no treatments or vaccines shown to be safe or effective for treating or preventing Ebola virus disease, and products currently under

development are in the very early stages of investigation for their respective indications. FDA is dedicated to do all that we can to respond effectively and rapidly to this epidemic.

FDA's Response to the Ebola Epidemic

This Ebola outbreak is an unprecedented global health and security crisis, and FDA is taking extraordinary steps to be proactive and flexible in our response. We have a critical role in helping to facilitate the development, manufacturing, and availability of investigational products for use against Ebola virus disease. In response to this urgent situation, FDA is actively working with Federal colleagues, industry, and international organizations to facilitate development, including the evaluation of safety and efficacy, of treatments and vaccines with the potential to help mitigate this epidemic.

Each Federal partner has a vital part to play in the global race to find therapeutic solutions to this deadly disease. FDA participates in a cross-cutting Federal workgroup that meets regularly to provide ongoing interactions between the different Federal participants. FDA provides scientific and regulatory advice to U.S. Government agencies that support medical product development, including the National Institute of Allergy and Infectious Diseases (NIAID) at the National Institutes of Health (NIH), the Biomedical Advanced Research and Development Authority (BARDA) in the Office of the Assistant Secretary for Preparedness and Response (ASPR), and the U.S. Department of Defense (DoD), to help speed their development programs. We are also closely coordinating our activities with the Centers for Disease Control and Prevention (CDC).

In addition, we are extremely engaged with multiple medical product developers to clarify regulatory requirements, provide input on pre-clinical and clinical trial designs (including the potential for clinical trials that could use a common protocol to test several products at once and

that can be conducted in affected countries and in the United States), and expedite review of data as they are received from product developers. As a result, it is generally recognized that investigational products, including vaccines, for Ebola are moving forward at an unprecedented pace. As part of the overall response, FDA is expediting the review of Ebola-related Investigational New Drug (IND) applications, which are required by law for FDA-regulated clinical trials of drugs and vaccines to proceed. For example, FDA reviewed IND applications for investigational Ebola vaccines in less than one week and, after such review, allowed them to proceed. NIAID, which is co-developing an Ebola vaccine with GlaxoSmithKline (GSK), has announced that it began Phase 1 clinical testing in early September of this year, and NewLink Genetics has announced beginning Phase 1 clinical trials of its Ebola vaccine candidate in October. We also continue to work closely with therapeutic product developers to speed development of their products. To augment diagnostic capacity, we have contacted several commercial developers—entities we know are capable of rapidly developing these types of diagnostic tests—and have encouraged them to work with us to quickly develop and make available such tests. Several entities have expressed interest and are now in discussions with FDA.

FDA also is collaborating with the World Health Organization (WHO) and working with several of our international regulatory counterparts, including the European Medicines Agency, Health Canada, and others, to exchange information about investigational products for Ebola. These efforts support regulatory collaboration to harmonize and accelerate development and have the potential to contribute to approval of medical products in the United States and in other nations. With this important goal in mind, FDA entered into a confidentiality commitment with WHO to allow the exchange of non-public information concerning medical products. We believe this will

facilitate international collaboration to respond to the Ebola epidemic, as well as more broadly to prepare for and respond to any future public health crises.

I have had the opportunity to participate in several WHO-sponsored consultations with my Federal colleagues, as well as representatives of the international public health community and medical product sponsors, to discuss the leading investigational treatments and vaccines for Ebola and key considerations for deployment in West Africa. These consultations are fostering a more coordinated and effective global public health response to the Ebola epidemic. Additionally, FDA scientists are providing technical advice to the WHO as they work to assess the role of convalescent plasma in ameliorating Ebola virus disease. Moving forward, FDA will continue working with our international colleagues to foster development of and access to investigational products in affected countries.

While FDA is making every effort to encourage development, speed review, and use flexible approaches to enhance the availability of potential medical products to address Ebola, it must be remembered that the investigational vaccines and treatments for Ebola are in the earliest stages of development. Data on effectiveness in humans are limited or lacking, and accurate assessment may be impossible if adequately designed clinical trials are not performed. In addition, the supply of some investigational products is limited. This supply issue constrains the options for properly assessing the safety and efficacy of these investigational products in clinical trials to respond to the epidemic, and also limits the possibilities for making products available for therapeutic use outside of a clinical trial (also known as expanded access). FDA is working with NIH to develop a flexible, innovative and adaptive clinical trial protocol that will provide a mechanism for product sponsors and investigators to evaluate multiple investigational products

under a common protocol. Our shared goal is to ensure accrual of interpretable data and generate actionable results in the most expeditious manner.

While investigational products are being developed, with the ultimate goal of approval of safe and effective products and manufacturing for wide-scale use, FDA is doing all it can to facilitate access to these products when access has been granted by the sponsor and the clinical circumstances warrant. FDA has one of the most flexible regulatory frameworks in the world, which includes mechanisms to enable access to investigational medical products when appropriate, after the risks and benefits to the patient have been weighed.

In addition, under the FDA's Emergency Use Authorization (EUA)[1] authority, we can allow the use of an unapproved medical product—or an unapproved use of an approved medical product—for a larger population during certain emergencies, when, among other reasons, sufficient preliminary data on potential risks and benefits are available for review and there is no adequate, approved, and available alternative. To date, FDA has authorized the use of six Ebola diagnostic tests (one developed by DoD, two developed by CDC, and three sponsored by commercial manufacturers). These diagnostic tests can help facilitate an effective response to the epidemic by rapidly identifying patients infected with Ebola virus and facilitating appropriate containment measures and clinical care. We were able to issue these EUAs, in part, because of new authorities gained under the Pandemic and All-Hazards Preparedness Reauthorization Act of 2013, or PAHPRA, which provide greater flexibility in the issuance of EUAs.

[1] Under the FD&C Act, as amended by the Project BioShield Act of 2004 [PL 108-276] and PAHPRA [PL 113-5], the Secretary of HHS has the authority to authorize FDA to permit the "emergency use" of medical countermeasures in certain situations [21 USC § 360bbb-3].

Unfortunately, during epidemics such as this, fraudulent products that claim to prevent, treat, or cure a disease rapidly appear on the market. FDA has learned of several fraudulent products that claim to prevent or treat Ebola virus infection. In response, we issued a statement, warning consumers about fraudulent Ebola treatment products, and we are taking actions against fraudulent claims to protect public health. For example, we issued Warning Letters to three firms marketing products that claim to prevent, treat, or cure infection by the Ebola virus.

EMERGENCY APPROPRIATIONS REQUEST

The Administration has requested an additional $6.18 billion to support the U.S. Government's international and domestic efforts to respond to the Ebola epidemic as well as efforts to develop medical products with the potential to help mitigate this epidemic. The request includes $25 million for FDA. This funding is necessary to enable FDA to sustain its aggressive efforts to support the pipeline of investigational medical products for Ebola and other serious emerging infectious diseases, including accelerating product development and review, facilitating access to investigational products, and supporting fraudulent product surveillance. This funding also will enable FDA to support and conduct the regulatory science research necessary to develop the tools, standards, and approaches to characterize investigational medical product safety, efficacy, quality, and performance that are so critical to expedite availability of medical products for Ebola.

CONCLUSION

FDA is fully committed to responding in the most proactive, thoughtful, and flexible manner. We have explored multiple ways to be highly responsive and adaptive to the complex range of

issues that this constantly changing epidemic has presented and will continue to present. FDA is using its authorities to the fullest extent possible to continue its mission to protect and promote the public health, both domestically and abroad.

Developing the medical products to help bring this Ebola epidemic under control is highly complex and will, unfortunately, take time. Close cooperation and collaboration within FDA, within the U.S. Government, with our international partners, and with product developers are essential to the global response to this epidemic.

Determining, as quickly as possible, whether the investigational drugs and vaccines being developed for the treatment and prevention of Ebola virus disease work have little effect, or actually harm patients is critically important. The only way to make that determination is through properly designed clinical trials.

FDA is fully committed to sustaining our deep engagement and aggressive response activities. We will continue to work closely with our U.S. Government and international partners and with product developers to speed the development and availability of promising medical products that offer the potential to help end this epidemic as quickly as possible. We fully appreciate the gravity of the situation at hand and are exercising maximum flexibility in our activities. We are singularly focused on facilitating and expediting the development of safe and effective medical products to diagnose, prevent, and treat Ebola virus disease.

Thank you, and I am happy to answer your questions.

Mr. PITTS. The Chair thanks the gentlelady.

Now recognize Admiral Redd for 5 minutes for an opening statement.

STATEMENT OF STEPHEN C. REDD

Mr. REDD. Good morning, Chairman Pitts, Ranking Member Waxman, and members of the subcommittee. It is a pleasure to be here to have the opportunity to describe the current epidemic of Ebola in West Africa, what CDC is doing to respond there as well as here in the United States, and I will talk briefly about the work we are doing to support vaccine evaluation in West Africa.

Ebola, since its identification in 1976, is the same disease. The situation is very different in West Africa from prior outbreaks, but the disease itself is similar with the same symptoms, the same incubation period, the same spread through infected bodily secretions, and control measures that are being implemented to identify, isolate, and treat cases and track contacts. Although the purpose of this hearing is countermeasures, as we have heard, their availability can't be assured in the immediate future, so, for the near term, we are going to be applying those traditional public health measures.

I would note that the administration has requested $1.83 billion for CDC to help respond to the Ebola outbreak. This is critical for three areas of work. The first is the immediate response in the affected countries, the highly affected countries, to extinguish the epidemic at its source. The second is to improve the ability in the U.S. to identify and treat cases. And the third is to increase the public health emergency response capabilities in vulnerable nations throughout the world, the Global Health Security Agenda.

In West Africa, as we have heard, there are slightly more than 15,000 cases right now that have been reported, 5,700 deaths. These have been spread through two primary means: exposure to secretions through unsafe care, either in the community or in medical settings, and through unsafe burials. The situation is different in the three most highly affected countries, but I would note that even in Liberia, where we have seen signs of leveling off, that there are still 200 to 300 cases being reported each week, so it is way too early to celebrate.

Two countries have controlled imported cases with stopping chains of transmission both in Senegal and in Nigeria. We are now working on a new situation in Mali. There are six cases that have involved two funerals and over 400 contacts that are being traced, and so we are very concerned about the situation in Mali right now. And with the end of the rainy season, there is increased possibility of spread to neighboring countries; particularly Cote d'Ivoire is a country of concern.

We used to say that this outbreak was bigger than all other outbreaks combined, but actually, in the past 2 weeks, there have been as many cases as there had been in all the previous outbreaks, and the current outbreak in West Africa is about 30 times larger than the largest previous outbreak.

I will turn now to U.S. preparedness. We have been working hard to prepare here before the first imported cases, and we have altered our plans as the situation has evolved. I will note just a

couple of things that we have implemented. There is inbound screening of passengers that have traveled from West Africa to the United States in five airports. All travelers from those countries have to pass through these airports. Mali has been added to that list as of this past Monday. Those individuals are tracked for 21 days, their entire potential incubation period, so that if they do develop symptoms, they can be routed quickly to a place that can diagnose them and treat them.

I will turn now just briefly to countermeasure development. As Dr. Fauci mentioned, there are vaccine trials being planned for West Africa. CDC is planning to work collaboratively with BARDA, FDA, and NIH on a trial in Sierra Leone using a different study design than the one that will be conducted by NIH. These are complementary and increase the chances of getting information on safety and effectiveness as quickly as possible.

I would just like to close with as long as there are cases in West Africa, there will be a risk of cases occurring in the United States. It is an important reminder that we are at risk when other countries lack basic capabilities. The administration's request underscores the urgent need to work in these vulnerable areas. I thank the committee for its interest in Ebola, and we hope to have your support with the emergency funding. That concludes my testimony.

[The prepared statement of Mr. Redd follows:]

House Energy and Commerce Committee

Subcommittee on Health

Examining Medical Product Development in the Wake of the Ebola Epidemic

November 19, 2014

Statement of RADM Stephen C. Redd, MD

Centers for Disease Control and Prevention

Good afternoon Chairman Pitts, Ranking Member Pallone, and members of the Subcommittee. Thank you for the opportunity to testify before you today and for your ongoing support for the Centers for Disease Control and Prevention's (CDC) work protecting Americans. I am Rear Admiral Stephen C. Redd, Senior Advisor on CDC's Ebola response. I appreciate the opportunity to be here today to discuss the epidemic of Ebola, as well as the work the CDC is doing to manage this epidemic and its consequences, both here in the United States and overseas. My testimony will provide you with an update on the epidemic, the important steps we are taking to protect Americans by actions here at home and by eliminating threats overseas, and describe the unfinished work that needs to be addressed through the Emergency Funding Request for Ebola.

Status of the Epidemic

We have diagnosed a total of four Ebola cases in the United States, two of which were in people returning from West Africa and two health care workers infected here. In addition to these four cases, our health care system has successfully treated five American patients with Ebola who were safely medically evacuated from West Africa. Unfortunately, earlier this week, a volunteer physician was

medically evacuated from Sierra Leone and died in the United States. Since August, we have evaluated and ruled out Ebola in scores of other cases in the United States.

The 21-day monitoring period has passed for all of the community contacts and health care workers who had been identified by public health workers as having had potential contact with the Ebola patients in Texas and Ohio. We continue to monitor numerous low- but not zero-risk hospital staff who treated Dr. Craig Spencer in New York City.

Although there are some promising signs in parts of Liberia, the epidemic continues to rage there and elsewhere in West Africa. Some of this progress could be attributable to the extensive work the United States Government and our partners have done to increase treatment and isolation, and safe burials. This week, with the assistance of the Commissioned Corps of the United States Public Health Service, we have opened a facility intended to treat any health care workers who become infected with Ebola. We hope this will facilitate additional health care workers volunteering to care for patients. We were encouraged that proven public health techniques allowed for the containment of the disease in Nigeria and Senegal. However, we do see a continued risk to other African countries, as evidenced by the introduction of Ebola into Mali. While there has been some progress in some parts of Liberia, there is a long way to go before this epidemic is contained and we are safe from the risk of it spreading.

Protecting Americans

From the time the situation in West Africa escalated from an outbreak to an epidemic, we have recognized that we will only have zero risk in the United States when we eliminate the threat in West Africa. We have instituted layers of protections for Americans, starting with rigorous screening of passengers leaving the affected countries. Here in the United States, we also have anticipated that a

traveler could arrive with the disease, and we prepared for this possibility by working closely with our state and local partners and with clinicians and health care facilities so that any imported case could be quickly contained. We have learned important lessons from the imported case in Dallas, which underscored the need to improve tracking of those exposed; adapt and strengthen our guidance; ensure rigorous adherence to protocols; improve readiness of American hospitals; and work closely across Federal, state, and local levels of government.

The first imported case of Ebola in the United States, diagnosed on September 30 in Dallas in a traveler from Liberia, required CDC and the Nation's public health system to rapidly respond with control measures. As far as we have seen in Africa and the United States, Ebola only spreads from people who are ill or who have died, or from their body fluids. The two primary means by which Ebola spreads are unsafe care (prior to and after health care facility admission) and unsafe burials. Cultural norms that contribute to the spread of the disease in Africa – such as burial customs – are not a factor in the United States. Ebola can be stopped with appropriate triage, rapid diagnosis, and meticulous infection-control practices in American hospitals. CDC applies the best science and lessons we are learning to inform our guidance and actions.

We have been constantly monitoring and improving our response in the United States, and will continue to do so. This begins with a layered approach to increasing safety. Before the traveler leaves for the United States, these precautions start with intensive airport exit screening in the affected nations, including temperature scanning for outbound passengers. CDC staff worked to implement this exit screening through on-site training and ongoing direction in the affected countries.

CDC and U.S. Customs and Border Protection (CBP) within the Department of Homeland Security (DHS) also have implemented a rigorous program of entry screening for travelers at risk of

carrying Ebola arriving in the United States. On October 11, entry screening began for passengers arriving at JFK airport and at four additional airports on October 16. The four additional U.S. airports are Newark, Washington-Dulles, Chicago-O'Hare, and Atlanta-Hartsfield International. On October 21, 2014, DHS announced that all travelers coming to the United States by air from Ebola affected countries will be required to enter the United States at one of the five airports where enhanced screening measures are implemented. Also, CDC and DHS announced that, effective Monday, November 17, entry screening would begin for travelers from Mali due to the evolving nature of outbreaks there. Screening includes an assessment for risk exposure and early signs of infection, and triage of passengers with clinical symptoms. With this assessment, appropriate public health actions can be determined and implemented, including movement restrictions when warranted.

On October 27, CDC updated its interim guidance for monitoring people potentially exposed to Ebola and for evaluating their intended travel, including the application of movement restrictions when indicated, and, consistent with this guidance, partnered with all 50 states to begin a program of active monitoring for 21 days for any individual arriving from West Africa. This monitoring program begins at the airport – where CBP and CDC obtain detailed contact information and provide passengers with detailed information on monitoring along with thermometers, health information, a log for temperature and symptoms, contact information for state health departments, and a wallet card to refer to in case of illness. Travelers with fever (all of whom have tested negative for Ebola) have used this information to contact the 24/7 hotlines every state has established and have been transported safely, and cared for safely, while an Ebola diagnosis was being ruled out. State and local authorities are provided contact information and a detailed risk assessment for passengers, allowing them to take steps to appropriately actively monitor those with potential Ebola risks.

CDC is committed to providing immediate support to the state and local health and public health officials. Within hours of confirming the cases of Ebola, CDC had a team of people on the ground in Dallas; in New York City, CDC had a team already on the ground assessing the hospital, and sent additional staff even before the patient's diagnosis was confirmed, in order to assist the capable teams from state health departments, local authorities, and hospital staff. We have worked side-by-side with state and local officials to do all we can to prevent transmission to others. CDC supported the state and local officials to monitor people who may have been exposed to Ebola in Texas, New York City, and Ohio. These individuals were tracked for 21 days for any signs of symptoms, and were quickly isolated if symptoms developed. And, as of November 7, all contacts in both Texas and Ohio are out of the 21 day period of monitoring for onset of illness.

We were deeply concerned to have learned of transmission of the Ebola virus from the first, or "index" patient in the United States, to two health care workers in Dallas. While we may never know exactly how these transmissions occurred, they demonstrated the need to strengthen the procedures for infection-control protocols which allowed for exposure to the virus. The care of Ebola can be done safely, but it requires meticulous and scrupulous attention to infection control, and even a single inadvertent slip can result in contamination. Based on experience in Dallas as well as at NIH and Emory University, we updated our guidance for the use of personal protective equipment in the assessment and treatment of Ebola in the United States. We recommended that facilities keep the number of workers who care for anyone with suspected Ebola to an absolute minimum. We recommended that the procedures that are undertaken to support the care of an infected individual be limited solely to essential procedures. We are recommending there be a full time individual who is responsible only for the oversight, supervision, and monitoring of effective infection control while an Ebola patient is cared for.

We will continue to evaluate and improve infection control and preparedness as we learn more in the United States and elsewhere.

We have taken additional steps to increase the preparedness of hospitals. CDC is leading teams of public health infection control experts to assess the readiness of hospitals. This endeavor prioritized geographic locations around the hospitals where increased screening was occurring at airports and continues in a strategic manner. By November 17, these teams had visited 41 hospitals in 12 states and the District of Columbia. Every hospital should have the ability to recognize the signs of a possible Ebola case and isolate that individual. Further, the Administration's emergency funding request includes resources for the Department of Health and Human Services to strengthen infection control to prevent spread of Ebola and other infectious diseases in the United States. CDC is also increasing training for health care providers, including web based seminars on donning and doffing of PPE, and in-person events, such as one held at the Jacob Javits Center in New York, which was broadcast live and attended in-person by more than five thousand people.

Additionally, CDC continues to build capacity in our states through the Laboratory Response Network (LRN). In addition to CDC's own world class laboratories, 31 LRN labs now have capacity to test for Ebola, increasing access to timely diagnosis – and surge capacity in case it is needed. CDC is also extensively consulted to support evaluation and, when indicated, test people who may have Ebola. With heightened alert, we are receiving hundreds of inquiries for help ruling out Ebola in travelers – a sign of how seriously airlines, border agents, public health departments, and health care system workers are taking this situation.

On November 5, the Administration proposed an emergency funding request, including $1.83 billion for CDC, to enhance our efforts to address the situation. This request includes $621 million designed to fortify domestic public health systems. This request allows us to fully implement the urgent strategies outlined above, and includes support for the following activities:

- Improve Ebola readiness within State and local public health departments and laboratories.
- Support state health departments to improve and accelerate infection-control implementation throughout U.S. hospitals.
- Procure personal protective equipment (PPE) for the Strategic National Stockpile.
- Increase support for monitoring of travelers at U.S. airports and in states and communities.

Eliminating Ebola in West Africa

CDC's top priority is to protect Americans from threats. In the case of Ebola, this means not only working here at home, but eliminating the risk to Americans by stopping this epidemic at its source in Africa.

The current epidemic in Guinea, Liberia, and Sierra Leone is the first time an outbreak has been recognized in West Africa, the first-ever Ebola epidemic, and the biggest and most complex Ebola challenge the world has ever faced. We have seen cases imported into Nigeria, Senegal, and Mali from the initially-affected areas and we have also seen in Nigeria and Senegal that proven practices such as contact tracing, monitoring, and isolation and care can prevent a small number of cases from growing into a larger outbreak. We are working intensively in Mali to apply these control measures.

The earliest recorded cases in the current epidemic were reported in March of this year in West Africa. Following an initial response that seemed to slow the early outbreak for a time, cases flared again due to weak health care and public health systems. As of earlier this week, the epidemic has reached 14,484 reported cases, including 5,524 documented deaths, though we believe these numbers are substantially below actual disease rates.

The health systems in the affected countries in West Africa were weak prior to the Ebola outbreak, and do not reach into rural areas effectively. Health care workers are often too few in number and not reliably present at facilities, and those facilities have limited capacity. Poor infection control in routine health care throughout West Africa, along with traditions such as public funerals and preparing bodies of the deceased for burial, make efforts to contain the illness more difficult. Furthermore, the porous land borders among these three countries and their neighbors in West Africa as well as remoteness of many villages have greatly complicated control efforts. The epidemic has further weakened these fragile health care systems – many of which are now essentially shuttered – and as a result local populations have lost access to treatment for other major health threats, such as malaria, diarrheal disease, and assistance with birth and delivery. The secondary effects of this outbreak also transcend the medical realm, as the economies of the affected countries have taken major blows that could impact their growth and development for years to come and greatly complicated the epidemic response. To stop an Ebola outbreak, we find active cases, respond appropriately, and prevent future cases. The use of diagnostics is important to identify new cases. Once active cases have been identified, we must support safe and effective patient care in treatment centers, prevent further transmission through proper infection control practices, and protect healthcare workers. Epidemiologists must identify contacts of infected patients and follow up with them every day for 21 days, initiating testing and isolation if symptoms emerge. And, we must intensify our use of health communication to disseminate messages about effective prevention and risk reduction. These messages include recommendations to report suspected cases, to

avoid close contact with sick people or the deceased, and to promote safe burial practices. In Africa, another message is to avoid unsafe handling of bush meat and contact with bats, since "spillover events," or transmission from animals to people, in Africa have been documented for other viruses similar to Ebola through these sources.

We are working to strengthen the global response, which requires close collaboration with the World Health Organization (WHO) and additional assistance from our international partners. At CDC, we activated our Emergency Operations Center to respond to the initial outbreak, and are surging our response. As of last week, CDC has over 177 staff in West Africa, and over 1,750 staff in total have provided logistics, staffing, communication, analytics, management, and other support functions. CDC will continue to work with our partners across the United States Government and elsewhere to focus on key strategies of response: effective incident management, isolation and treatment facilities, safe burial practices, infection control throughout the health care system, and communications.

The public health response to Ebola rests on the same proven public health approaches that we employ for other outbreaks, and many of our experts are working in the affected countries to rapidly apply these approaches and build local capacity. These include strong surveillance and epidemiology, using real-time data to improve rapid response; case-finding and tracing of the contacts of Ebola patients to identify those with symptoms and monitor their status; and strong laboratory networks that allow rapid diagnosis.

The Administration's proposed emergency funding request includes $603 million for CDC efforts to control the epidemic in the hardest hit countries in Africa by funding activities including: infection control, contact tracing and laboratory surveillance and training; emergency operation centers and

preparedness; and education and outreach, and to conduct clinical trials in affected countries to assess safety and efficacy of vaccine candidates.

Reinforcing Basic Global Health Protections

There is an urgent need to reinforce basic public health systems in countries, such as those in West Africa, where disease threats can quickly arise and ultimately threaten the health of Americans. The Emergency Funding Request will allow us to emergently address unanticipated, urgent threats to health and global stability. We believe that if basic lab networks that can rapidly diagnose Ebola and other threats, emergency operations centers that can swing into action at a moment's notice, networks of trained disease detectives who can find an emerging threat and stop it quickly, and surveillance systems had been in place in West Africa before the current outbreak, the epidemic could have been prevented. Building these capabilities at the places of highest risk is key to preventing this type of event elsewhere and to ensuring that countries are prepared to deal with the consequences of their own outbreaks before they are exported to other countries. We must do more, and do it quickly, to strengthen global health security around the world, because we are all connected. Diseases can be unpredictable – such as H1N1 coming from Mexico, MERS emerging from the Middle East, or Ebola in West Africa, where it had never been recognized before – which is why we have to be prepared globally for anything nature can create that could threaten our global health security.

The Administration's proposed emergency funding request includes $606 million for CDC to strengthen global health security, reducing risks to Americans by addressing unanticipated threats and enabling the world to detect them early, respond swiftly before they become epidemics, and prevent outbreaks wherever possible. These efforts will provide temporary assistance to establish global health security capacity in vulnerable countries to prevent, detect, and rapidly respond to outbreaks before they become

epidemics by standing up emergency operations centers; providing equipment and training needed to test patients and report data in real time; providing safe and secure laboratory capacity; and developing a trained workforce to track and end outbreaks before they become epidemics. These activities are necessary to combat the spread of Ebola and reduce the potential for future outbreaks of Ebola and other infectious diseases that could follow a similarly devastating, costly, and destabilizing trajectory.

Conclusion

Stopping Ebola will take time and meticulous work. There are no short cuts. It's like fighting a forest fire: leave behind one burning ember, one case undetected, and the epidemic could re-ignite. For example, in response to the case in Nigeria, 10 CDC staff and 40 top CDC-trained Nigerian epidemiologists rapidly activated, identified contacts, and worked with more than 1,000 Nigerian health workers to track 899 contacts for 21 days, making 19,000 home visits. Even with these resources, one case was missed, which resulted in a new cluster of cases in Port Harcourt, Nigeria. The health care workers persevered, and Nigeria is now Ebola-free – from that importation event. Public health strategies can stop transmission of Ebola and halt the progression of an outbreak.

With a focused effort, and increased vigilance at home, we can stop this epidemic, protect Americans, and leave behind a strong system in West Africa and elsewhere to prevent Ebola and other health threats in the future.

Thank you again for the opportunity to appear before you today. I appreciate your attention to this epidemic and I look forward to answering your questions.

Mr. PITTS. The Chair thanks the gentleman.

Now recognize Dr. Robinson 5 minutes for an opening statement.

STATEMENT OF ROBIN A. ROBINSON

Mr. ROBINSON. Good morning, Chairman Pitts, Vice Chairman Burgess, Vice Chairwoman Blackburn, and Ranking Member Waxman, and distinguished members of the subcommittee. Thank you for the opportunity to speak with you today about our Government's Ebola response efforts. BARDA, created by the Pandemic and All-Hazards Preparedness Act in 2006, is the Government agency with the full-time responsibility to support advanced development and procurement of novel and innovative medical countermeasures, such as vaccines, therapeutic drugs, diagnostics, and medical devices for the entire Nation. I am here today to update you on the progress that we have made on Ebola medical countermeasure response activities.

BARDA has used several overarching principles to guide us through previous public health emergencies, like the H1N1 pandemic, H7N9 outbreaks in China last year, and is now applying them to the current Ebola epidemic response.

First, BARDA exists to address the medical consequences of biothreats and emerging infectious diseases. Ebola represents both.

Second, BARDA works with our Federal partners here to transition medical countermeasures from early development into advanced development towards ultimate FDA approval. Today, BARDA has transitioned one Ebola therapeutic candidate and three Ebola vaccine candidates from early development in NIH and DOD into advanced development with three more therapeutic candidates and one more vaccine candidate under consideration.

Third, BARDA, in concert with our Federal partners, utilizes public-private partnerships with industry to ensure that we have countermeasures to protect our citizens. Today we are working with both small and large biotechnology and pharmaceutical companies in public-private partnerships, collaborating with other countries and NGOs, and providing actual staff to help WHO in their efforts.

BARDA, fourthly, has established a medical countermeasure infrastructure to assist product developers on a daily basis and to respond immediately in a public health emergency. To name a few, today BARDA is utilizing our nonclinical studies network to conduct critical animal challenge studies to evaluate new Ebola monoclonal antibody and therapeutic candidates; our Centers for Innovation in Advanced Development and Manufacturing to expand production of Ebola monoclonal antibodies as they become available; our Fill Finish Manufacturing Network to fill both Ebola antibody and vaccine products into vials; our new Clinical Studies Network to help CDC plan and conduct vaccine clinical trials in Sierra Leone early next year, as Dr. Redd said; and our modeling unit to coordinate Federal and international modeling efforts for evolving Ebola epidemiology and interventions. These investments that you and we have made since 2010 to create this infrastructure are now playing a major role in the Nation's response to the current Ebola epidemic.

BARDA supports large-scale production of medical countermeasures as a response measure for public health emergencies. Today BARDA is working with our industry partners to scale up production of Ebola vaccines and monoclonal antibodies to ensure commercial scale manufacturing will be possible when needed. Specifically, we have implemented a three-pronged approach to maximize the production of promising Ebola monoclonal antibodies, like ZMapp. First, we awarded a contract in September to Mapp Biopharmaceuticals for development and manufacture of ZMapp produced by Kentucky Bioprocessing using tobacco plant-based technologies. This product candidate has been provided to non-Ebola infected persons under an EID with FDA's assistance. Efforts to optimize production have already seen a nearly twofold increase in production yield, and the clinical trials for this product are on track to start in January 2015 being conducted by the NIH.

Because the present manufacturing process is at pilot scale, we are expanding manufacturing capacity by enlisting the help of other tobacco plant biopharmaceutical companies, including those associated with ADMs.

Lastly, we are trying to increase antibody production by partnering with several companies, including Genentech and Regeneron, who make monoclonal antibodies at commercial scale routinely for other diseases and have developed innovative state-of-the-art monoclonal antibody technologies and mammalian cells. We are on track now to test these new Ebola antibodies early next year in animals and, if successful, in human clinical trials shortly thereafter. Additionally, we will weigh the results of ongoing NIH animal challenge studies to determine whether we support advanced development of two Ebola antiviral drug candidates.

With respect to vaccines, BARDA is supporting the development of several vaccine candidates from Profectus for clinical trials next year and NewLink Genetics for product development and commercial scale-up manufacturing. With additional funds, we will be able to support commercial manufacturing scale up and further clinical trials for other promising Ebola vaccine candidates from GlaxoSmithKline, Johnson and Johnson, and Bavarian Nordic to ensure we have vaccines when they are needed.

Finally, together, we face significant challenges in the coming weeks and months as the Ebola epidemic evolves, clinical trials start, and manufacturing improvements are implemented. Be assured, we are doing all that can be done, and I thank you for your help over the years, and I look forward to your questions. Thank you.

[The prepared statement of Mr. Robinson follows:]

Written Testimony
Committee on Energy and Commerce
Subcommittee on Health
United States House of Representatives

"Examining Medical Product Development in the Wake of the Ebola Epidemic: The Biomedical Advanced Research and Development Authority's Response"

Statement of
Robin A. Robinson, Ph.D.
Deputy Assistant Secretary and BARDA Director
Office of the Assistant Secretary for Preparedness and Response
U.S. Department of Health and Human Services

ASPR
ASSISTANT SECRETARY FOR PREPAREDNESS AND RESPONSE

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Good morning, Chairman Pitts, Ranking Member Pallone, and distinguished Members of the Subcommittee. Thank you for the opportunity to speak with you today about our Government's Ebola epidemic response efforts. I am Dr. Robin Robinson, Director of the Biomedical Advanced Research and Development Authority (BARDA) and Deputy Assistant Secretary to the Assistant Secretary for Preparedness and Response (ASPR) of the Department of Health and Human Services (HHS).

Ebola is simultaneously a biothreat and an emerging infectious disease. The current Ebola epidemic is the worst on record. As the Centers for Disease Control and Prevention (CDC) has stated, we do not view Ebola as a significant public health threat to the United States; however, the best way to continue to protect our country from any domestic threat posed by Ebola is to take action to address the epidemic in West Africa with robust infection control measures and possibly vaccination.

ASPR is supporting the Federal Government's Ebola response effort through policy development, advancements in medical countermeasures (MCM), logistical support for deployed personnel, and broader community and health care preparedness and resilience through grant funding, dissemination of information to state and local partners, and communication with international partners concerning health security issues. Originally authorized by the Pandemic and All-Hazards Preparedness Act (PAHPA) in 2006 and then reauthorized in 2013, ASPR leads the country in preparing for, responding to, and recovering from the adverse health effects of emergencies and disasters by supporting

communities' ability to withstand adversity, strengthening our health and response systems, and enhancing national health security.

Last year, the Pandemic and All-Hazards Preparedness Reauthorization Act of 2013 (PAHPRA) reauthorized many programs and authorities within ASPR to improve preparedness, response, and recovery activities. ASPR is currently implementing the provisions required in PAHPRA. Programs authorized under PAHPRA build on successes from the original legislation in 2006 as well as lessons learned.

ASPR is comprised of six supporting offices. All six are working together closely to leverage resources, target communications, and enhance coordination at Federal, state, and local levels as well as internationally. Three of ASPR's offices are the Office of Policy and Planning (OPP), which supports development of policy options during this response, as well as international public health emergency preparedness and response activities; the Office of Emergency Management (OEM), which is responsible for the Secretary's Operations Center, supports all operations, logistics and deployment, and our regional activities, as well as the Hospital Preparedness Program; and BARDA.

BARDA is the Federal Government Agency mandated to support advanced research and development and procurement of novel and innovative MCMs such as vaccines, antimicrobial drugs, diagnostics, and medical devices for the entire Nation to address the medical consequences of chemical, biological, radiological, and nuclear (CBRN) agents

of terrorism. It also addresses naturally-occurring and emerging threats like the H1N1 pandemic, last year's H7N9 influenza outbreak, and the current Ebola epidemic.

BARDA exists to address the medical consequences of these threats and to bridge the gap between early research and development and eventual Food and Drug Administration (FDA) approval and procurement of MCMs for novel threats by supporting advanced research and development of MCM candidates. Advanced development includes critical steps needed to transform a candidate to a product that is ready to use. These steps include optimizing and validating manufacturing processes such that products can be made at commercial scale; optimizing product formulation for optimum field usage, storage, and product longevity and effectiveness; creating and optimizing assays to assure product integrity; conducting late-stage clinical safety and efficacy studies; and carrying out pivotal animal efficacy studies that are often required for approval. Since 2006, BARDA has funded and successfully managed the advanced development of more than 150 MCMs for CBRN threats and pandemic influenza. Seven of these products have received FDA approval in the last two years alone, and twelve of these products have been made available for use under Project BioShield.

Over the last decade, the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) has supported basic research and early stage development of numerous Ebola and Marburg virus MCM candidates. BARDA is now coordinating with, providing funding, and providing technical assistance for the development and scaled-up manufacturing of the ZMapp monoclonal antibody therapeutic and several Ebola vaccine

candidates that the National Institutes of Health's (NIH) National Institute of Allergy and Infectious Diseases (NIAID) and the Department of Defense's (DoD) Defense Threat Reduction Agency (DTRA) supported through early development. BARDA aims to ensure that these MCM candidates are available for clinical evaluation for safety and efficacy as soon as possible and that these products can be manufactured reproducibly and robustly at commercial scale in a controlled manner to produce large enough quantities for use in a meaningful public health response. Ultimately, we strive with our partners to have these MCMs approved by the FDA as soon as it is feasible, if results of these clinical evaluations so warrant.

Specifically, BARDA, along with its PHEMCE partners, uses public-private partnerships with industry to ensure that we have the MCMs to protect the national health security of the United States in emergencies. Over the past five years, BARDA—with NIH, CDC, FDA, and industry partners—has built a flexible and rapidly-responsive infrastructure to develop and manufacture MCMs. Last year, for example, in response to the H7N9 influenza outbreaks in China, the PHEMCE mobilized these partnerships to design, develop, manufacture, clinically evaluate, and stockpile several vaccine candidates in record time. In the current Ebola response, BARDA is working with a wide array of partners that include other countries, specifically the affected and at-risk African countries; the World Health Organization (WHO); the Bill and Melinda Gates Foundation; and others. These expanded partnerships are critical to our efforts to address the current Ebola epidemic.

BARDA has established an MCM infrastructure to assist product developers on a daily basis and enable rapid response in a public health emergency. We are now employing this infrastructure to respond to the current Ebola epidemic by expediting the rapid development and manufacturing of several investigational Ebola therapeutics and vaccines. BARDA's Nonclinical Studies Network is conducting critical animal challenge studies on several promising investigational Ebola monoclonal and small molecule therapeutic candidates that may be developed further. Established in 2012, BARDA's Centers for Innovation in Advanced Development and Manufacturing are working to expand the production of Ebola monoclonal antibodies, like those in ZMapp. Last year, as part of its pandemic preparedness efforts, BARDA established the Fill Finish Manufacturing Network, which is now being used to formulate and fill multiple Ebola antibody and vaccine candidates into vials for the potential clinical efficacy studies in West Africa. Our new Clinical Studies Network is working with CDC to conduct vaccine clinical trials in Sierra Leone. BARDA is coordinating Federal and international modeling efforts for Ebola epidemiology and interventions as domestic and international scenarios and capabilities evolve. The investments that we have made since 2010 to create this infrastructure are playing a major role in the Nation's response to the current Ebola epidemic.

BARDA also supports large-scale production of MCMs as an essential part of the response to public health emergencies. BARDA led the manufacturing of vaccine and antiviral drugs in response to the H1N1 pandemic in 2009 and of vaccines as a preparedness measure for H7N9 outbreaks in 2013. In the current Ebola epidemic,

BARDA is providing assistance to vaccine and therapeutic manufacturers to scale-up production from pilot scale, in which a handful of doses can be made, to commercial scale, producing millions of doses.

For Ebola immunotherapeutics, as previously mentioned, BARDA is supporting the development and manufacturing of Mapp Biopharmaceutical's ZMapp monoclonal antibody combination therapeutic candidate, which was provided over the past three months to several Ebola patients under emergency Investigational New Drug applications. That drug is currently being manufactured to provide sufficient doses for the initial clinical safety and efficacy studies in Ebola-affected countries in West Africa. Furthermore, BARDA has enlisted the help of Genentech and Regeneron to develop Ebola monoclonal antibody therapeutic candidates rapidly using state-of-the art monoclonal antibody technologies and mammalian cells capable of immediate commercial scale production. With funds from the President's Emergency Request, we can expand production capacity to other domestic manufacturers and produce larger quantities of Ebola monoclonal antibodies using tobacco plants or mammalian cells. Such funding will also enable BARDA to support advanced development and manufacturing of two additional Ebola therapeutic candidates, if current NIH animal challenge studies yield favorable results.

With respect to vaccines, BARDA is supporting the development of a vaccine candidate (rVSVN4CT1 EBOV) from Profectus in clinical trials next year and is working with NewLink Genetics to develop and scale-up the manufacturing of their promising

investigational Ebola vaccine candidate (rVSVΔG EBOV) to commercial scale. However, additional funds are needed to support commercial manufacturing scale-up of other promising Ebola vaccine candidates from NIAID/GlaxoSmithKline, Johnson & Johnson, and Bavarian Nordic to ensure that additional vaccines are available for clinical trials and vaccination campaigns, if needed.

BARDA and its Federal and industry partners are fully engaged in the development and manufacture of these Ebola MCM candidates in record time. The immediate challenge is being able to provide sufficient quantities early enough to support clinical studies and ensuring that commercial scale manufacturing processes are robust enough to support mass usage. BARDA is prepared to meet those challenges and provide resources, expertise, and technical assistance for these and other promising investigational Ebola vaccine and therapeutic candidates. We are working with our partners across the Federal Government, new and existing industry partners, and international partners including the WHO, non-governmental organizations, West African countries, and other allied donor nations to meet these challenges.

In addition to BARDA's efforts in the Ebola response, ASPR is supporting a number of other response activities including: supporting health care system preparedness through the Hospital Preparedness Program (HPP); developing policies and guidance on patient movement, repatriation, standards of care, and clinical guidance; supporting the logistical aspect of deploying U.S. Public Health Service (USPHS) officers to West Africa; and,

ongoing critical coordination and communication within the national and international communities responding to the threat.

Beginning with efforts to support health care system preparedness, over the past 12 years, state and local health departments have purchased health care facility-based equipment and supplies, exercised and trained for a number of different emergency scenarios, including highly infectious diseases, and developed partnerships and coalitions across regional health care systems to address situations just like Ebola by utilizing HPP grant funding. Through the HPP grant, ASPR is supporting domestic preparedness by producing and disseminating educational materials on awareness and response to potential Ebola patients. It is working to ensure state and local partners have relevant information to understand the emerging situation and have the right protocols and procedures in place to mitigate the threat. Specifically, HPP, along with other ASPR and HHS partners, including CDC, helped develop and disseminate checklists to prepare health care providers, hospitals, emergency medical services, and community health care coalitions.

HPP is helping CDC recruit U.S. hospitals that are willing and able to care for confirmed cases of Ebola among U.S. citizens who are medically evacuated to the United States from the affected countries in West Africa. Finally, HPP awardees may use their current HPP funds to prepare for suspected or known Ebola patients, including the development of action plans, purchase of supplies for health care facilities, and training for all personnel. In emergency circumstances, HPP awardees may request approval to use

grant funds for activities outside the currently approved scope of work. Some awardees have already initiated these requests.

We understand there is a high demand nationwide for personal protective equipment (PPE) to prepare for and respond to domestic Ebola cases, and that PPE suppliers are experiencing significant backorders for some products. ASPR has formed a PPE supply chain workgroup of departments and agencies to coordinate the Federal Government's response to this situation. The workgroup is in regular discussions with PPE manufacturers and distributors to assess the availability of products and to develop strategies to address supply chain challenges.

ASPR is working with CDC and the Association of State and Territorial Health Officials to identify hospitals willing to accept Ebola patients via medical evacuation and is also engaged with government-wide partners to resolve Ebola-related waste removal concerns. In collaboration with other HHS colleagues, ASPR and CDC developed Ebola Medical Waste Management guidelines with input from the Department of Transportation, the Environmental Protection Agency, and the Occupational Safety and Health Administration, providing hospitals and health care providers with key guidance to safely handle, transport, and dispose of waste generated from the care of persons diagnosed with or suspected of having Ebola.

Regarding the international response, ASPR, through its international health security efforts, continues to receive and share information with the WHO and countries around

the world about Ebola. In addition, ASPR maintains regular communications and coordination with G7 countries, Mexico, and the European Commission on public health measures, development and deployment of MCMs, and support for West African countries.

In order to ensure that appropriate Federal resources are brought to bear in our international and domestic fight against Ebola, on November 5, the Administration proposed an emergency funding request totaling $6.18 billion, including $2.43 billion for HHS. As the Congress considers this request, I want to highlight some of the ways these funds would impact ASPR programs. All in all, $323 million would apply to ASPR activities. BARDA's additional funding would be used to support advanced development and manufacturing of Ebola vaccine and therapeutic candidates. OEM's additional funding would allow supplemental HPP grants for PPE purchases, for training, and for renovation, construction, and retrofitting facilities to create isolation units and separate laboratories.

In conclusion, we have established a solid track record in developing and manufacturing MCMs and coordinating successful emergency responses. ASPR, in coordination with the rest of the PHEMCE, is using all of its capabilities to address the Ebola epidemic in West Africa, and has identified crucial courses of actions that can be supported through the end of FY2015. These investments in Ebola MCMs and response will not only address the current epidemic and any future Ebola outbreaks, but will also help the United States to become better prepared to defend against bioterrorism.

Again, I would like to thank the Subcommittee for its generous and continued support and for the opportunity to testify. I look forward to your questions.

Mr. PITTS. The Chair thanks the gentleman.

That concludes the opening statements.

I have a UC request to put in the record a letter from Novavax and an article from the New England Journal of Medicine.

Without objection.

[The information follows:]

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House Energy & Commerce Committee
Subcommittee on Health
Examining Medical Product Development in the Wake of the Ebola Epidemic
November 19, 2014
Testimony: Novavax, Inc.

Chairman Pitts, Ranking Member Pallone, Members of the Committee, thank you for the opportunity to provide written testimony on behalf of Novavax, Inc. regarding our efforts to respond to the current Ebola crisis by rapidly advancing the development and production of a promising vaccine candidate.

Novavax is a clinical-stage biopharmaceutical company based in Maryland, focused on the discovery, development and commercialization of recombinant nanoparticle vaccines and adjuvants. Our principal vaccine candidates currently in clinical development include the world's most advanced vaccine for respiratory syncytial virus ("RSV") and vaccines against seasonal influenza and pandemic influenza, all of which are in Phase 2 clinical trials.

At Novavax, we use our technology to produce vaccine candidates that can rapidly respond to emerging diseases. For example, under our $179 million HHS/BARDA contract, we have developed and delivered compelling safety and immunogenicity data in humans for vaccines against two pandemic influenza strains: H5N1 and H7N9. We also have been monitoring other emerging diseases, such as Middle East Respiratory Syndrome (known as "MERS"), a novel coronavirus first identified in September 2012, as well as the recent outbreak of Ebola virus disease in West Africa.

It is worth noting that five (5) strains of Ebola have been identified, and that the strain currently afflicting West Africa is known as the "Guinea strain", which was identified in August 2014. With the speed and flexibility of our platform, we have been able to customize our vaccine to the currently circulating strain. While current publicly known vaccine approaches target earlier strains of the virus, Novavax' Ebola vaccine candidate is the first, and currently only, reported Ebola vaccine produced using the genetic sequence of the Guinea strain. Our Ebola vaccine has recently been successfully tested in both rodent and rabbit pre-clinical models. We have also tested the vaccine with our Matrix-M™ adjuvant in these same pre-clinical models, with results showing that Matrix-M appears to significantly contribute to enhanced immunogenicity and induction of neutralizing antibodies.

Due to the urgent global public health need for an Ebola vaccine, Novavax feels that it important to further develop our Ebola vaccine candidate. Therefore, we recently publicly announced our initiation of a non-human primate study and our expectation to initiate a Phase 1 clinical trial that will evaluate the safety and immunogenicity of our vaccine candidate in ascending doses, with and without our Matrix-M adjuvant. Subsequent clinical studies will be designed following the data from the non-human primate study and the Phase 1 clinical trial.

Despite heroic efforts by numerous global health agencies and product developers, development of vaccination strategies for emerging pathogens like Ebola are particularly challenging because of the sudden emergence and rapid dissemination of such diseases, as well as the long process of traditional vaccine development. Although the U.S. government is working with health agencies and industry players to stream-line and fast-track regulatory requirement, the U.S. government should also prioritize appropriations for vaccine platform technologies that are rapidly adaptable to novel and re-emerging pathogens. Novavax offers the following recommendations to the U.S. government:

1. **Invest in Flexible, Rapid and Proven Vaccine Technologies.** An effective response requires willingness to adopt vaccine technologies that demonstrate flexibility to make the first doses available on a rapid timeline from the identification of pathogen to first doses available.

   This approach would also minimize time and investment dollars in future emergencies. For example, Novavax' technology allows us to monitor reports concerning emerging diseases and, as soon as the genetic sequence of the pathogen is published, proceed from gene to human clinical data in comparatively short periods of time.

   Novavax demonstrated this capability last year in response to the H7N9 pandemic influenza strain, which was first recognized by Chinese health authorities as a potential pandemic influenza threat in late March 2013. In a three-month period, we developed a vaccine antigen, conducted multiple animal studies and initiated the world's first Phase 1 clinical trial of a vaccine against an H7N9 influenza strain. Our clinical results were published in November 2013 in *The New England Journal of Medicine*, where we showed that we achieved protective levels from vaccinations within just 116 days of the announcement of the H7N9 outbreak.

   Similarly, we have cloned the current Guinea strain of Ebola now circulating in West Africa, and we expect to be in a clinical trial soon. Our platform affords the U.S. government the opportunity to address not only Ebola, but other emerging infectious diseases, with a timely response that we believe can minimize future risks, as well as expenditures, for the benefit of citizens of the United States and the world.

2. **Invest in Scalable Technologies.** Technology that can rapidly produce the first doses of vaccine is critical, but effective vaccine platforms must also be rapidly scalable to produce sufficient vaccine to move through the development process and be deployed for effective use. As was seen with the antibody therapeutic developed by ZMapp, promising solutions can be handicapped by the lack of expandable production processes. The Novavax platform uses insect cell culture and disposable manufacturing equipment, both of which have proven to be rapidly scalable, to produce thousands up to potentially millions of vaccine doses within a matter of months.

3. **Continue to Invest in Adjuvant Technologies to Expand Supply and Broaden Protection.** Vaccines for highly pathogenic viruses, such as Ebola, should be made rapidly and in conjunction with the use of adjuvants. Adjuvants are immunostimulating molecules, designed to do one or more of the following: (1) improve the immunogenicity (i.e., to increase protection), (2) provide antigen dose-sparing (i.e., lower antigen doses increase number of doses available for distribution), and (3) broaden the scope of protection (e.g., cross-strain protection) as pathogens change and mutate. Several NIH and BARDA funded programs for pandemic influenza vaccines have demonstrated the significant dose-sparing potential of adjuvants when combined with vaccines. Novavax' own pandemic influenza program has demonstrated that certain adjuvants provide both immunogenicity and dose-sparing benefits compared to unadjuvanted vaccines. Moreover, Novavax pandemic influenza vaccines have demonstrated that certain adjuvants contribute to the broader cross-reactivity to different strains of pandemic influenza.

   Given the concern about manufacturing sufficient numbers of doses in a timely manner, Novavax recommends that the U.S. government support the development of Ebola vaccines with dose-sparing adjuvants so more vaccine doses can be available in less time.

Novavax has demonstrated the ability to rapidly and successfully advance vaccine candidates from gene sequence to clinical trials. We are currently committing our own human and technological capital in order to demonstrate our Ebola vaccine is worthy of consideration as a possible solution for this immediate health crisis. In addition, our platform technology can provide cost-effective and timely solutions to address future emerging disease threats.

Such efforts necessitate that the U.S. government ensures that emergency programs for Ebola products continue to be funded, but at the same time the U.S. government should evaluate the available technologies to address its longer-term needs to develop solutions to future emerging threats. Novavax agrees with BIO that to prepare for the full range of potential threats, we must prioritize funding for Project BioShield, BARDA, pandemic influenza, the SNS, and other programs that are essential to public health preparedness this year and in coming years. These programs simply cannot be funded only after a disaster hits; such reactionary thinking would put lives at risk. The U.S. biotechnology industry is uniquely capable of advancing early scientific innovations to products that can be safely and effectively used, and it is time to make the necessary investments to address Ebola and other newly emerging, novel infectious diseases with investments in companies capable of making new vaccines, such as Novavax.

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

Ebola Vaccine — An Urgent International Priority

Rupa Kanapathipillai, M.D., Ana Maria Henao Restrepo, M.D., Patricia Fast, M.D., Ph.D., David Wood, Ph.D., Christopher Dye, D.Phil., Marie-Paule Kieny, Ph.D., and Vasee Moorthy, B.M., B.Ch., Ph.D.

With the Ebola epidemic in West Africa continuing to grow, the World Health Organization (WHO) convened an urgent meeting on September 29 and 30 to assess the efforts under way to evaluate and produce safe and effective Ebola vaccines as soon as possible.[1] The 70 scientists, public health officials, and representatives from industry and regulatory bodies who gathered in Geneva discussed two vaccine candidates at length — cAd3-EBOV (cAd3), from GlaxoSmithKline (GSK) and the U.S. National Institute of Allergy and Infectious Diseases (NIAID), and rVSVΔG-EBOV-GP (rVSV), from NewLink Genetics and the Public Health Agency of Canada. Several other vaccine candidates are at earlier, preclinical stages in the development pipeline.

Phase 1 studies of cAd3 have begun in the United States and the United Kingdom, and researchers plan to begin enrollment for trials of rVSV soon. Both vaccine candidates have demonstrated 100% efficacy in studies in nonhuman primates,[2,3] but how that will translate to human subjects remains unknown. The phase 1 trials of both vaccines use dose–response designs structured to determine the level of humoral and cellular immunity that can be induced. The minimum antibody titer needed to confer protection in humans is unknown. Because of the small numbers of participants in these trials, they will provide data only on common adverse events.

The cAd3 vaccine is being tested in both bivalent (ClinicalTrials.gov number, NCT02231866) and monovalent (NCT02240875) forms; the monovalent form is based on the Zaire strain of Ebola virus, which is the cause of the current West African epidemic, and the bivalent form includes the Sudan strain of the virus as well (see Fig. 1). The monovalent form will be evaluated in a nonrandomized, open-label study involving 60 adult volunteers who will receive the vaccine at three different doses (1×10^{10} vp, 2.5×10^{10} vp, and 5×10^{10} vp). The bivalent form will be evaluated in a nonrandomized, open-label study involving 20 adult volunteers who will receive the vaccine at two different doses (2×10^{10}PU and 2×10^{11}PU). Both studies will assess safety, side effects, and immunogenicity, including antibody responses as measured by enzyme-linked immunosorbent assay (ELISA) and neutralization assays and T-cell immune responses as measured by intracellular cytokine staining. Investigators anticipate that pre-

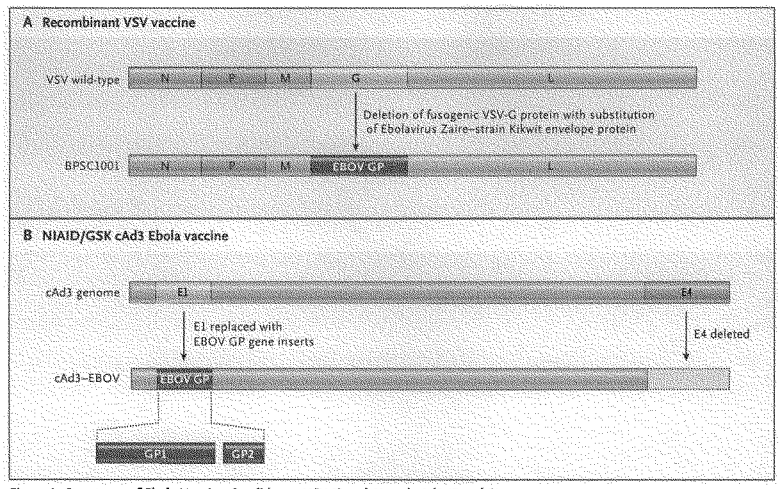

Figure 1. Structures of Ebola Vaccine Candidates rVSV (Panel A) and cAd3 (Panel B).

liminary immunogenicity and safety data will be available by November.

The first phase 1 trial of the rVSV vaccine is slated to begin soon in the United States. Ideally, the immunogenicity outcomes in this trial will be compared with those obtained with the GSK–NIAID vaccine. The government of Canada has donated 800 vials of rVSV to the WHO, and discussions about expanding phase 1 trials to European and sub-Saharan African sites are at an advanced stage.

Participants in the Geneva meeting stressed that phase 1 trials should be expedited and their results shared broadly in order to facilitate rapid progression to phase 2. If the results in phase 1 are favorable, the consensus was that phase 2a studies should be conducted in Africa but outside the current Ebola outbreak zone and should proceed in parallel with phase 2b studies conducted in exposed populations. This approach will provide robust efficacy and safety data as quickly as possible. Results from phase 2a trials in unexposed populations would inform the use of these vaccines in expanded populations, including children and people who are HIV-positive. The phase 2b trials in exposed populations would enroll people who are at the highest risk for Ebola virus disease, including frontline workers at Ebola treatment facilities.

The design of these proposed trials in exposed populations raises many complex questions that pit issues of scientific rigor against feasibility and acceptability. Since there are no data on the efficacy of Ebola vaccines in humans, equipoise justifies the use of a randomized, controlled trial. Yet though it's clear that well-designed randomized, controlled trials would generate the most reliable and robust data regarding vaccine efficacy, the feasibility of such studies may be affected by the same fear and resistance to interventions that communities have evinced in the West African epidemic to date. The trials therefore need to be designed with participation from local governments and communities so that they can proceed in a manner that is acceptable to the affected populations. The consensus at the Geneva meeting was that there are reasonable alternatives if individually randomized, controlled trials are not acceptable in some settings — for example, studies using a stepped-wedge design (see Fig. 2). A basic principle of every study design should be that all participants will receive Ebola vaccine at some point. There was also agreement that health care workers who care for patients with Ebola or are otherwise exposed to patients' body fluids in hospitals and clinics, family members

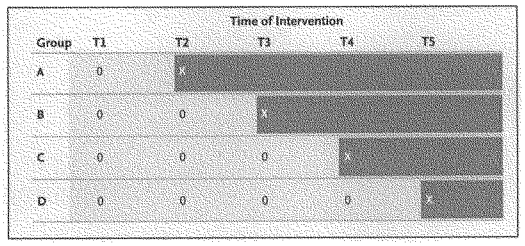

Figure 2. Stepped-Wedge Study Design Schematic.

Participants are randomly assigned to receive the intervention at one of several times. Outcomes in each group are measured at each step. X denotes the intervention, and O control treatment.

caring for patients with Ebola at home, and people who cleanse and bury deceased patients should be among those given the opportunity to participate in the early phase 2 trials.

Representatives of regulators and ethics committees in Africa as well as of the U.S. Food and Drug Administration and the European Medicines Agency were at the meeting and agreed to work with industry and researchers to accelerate the evaluation, licensure, and availability of the candidate vaccines. The regulators stressed that rigorous standards for clinical safety and efficacy will be applied. Another WHO-arranged meeting is planned for November to reevaluate the next necessary steps once preliminary results from the phase 1 trials are available.

Even if adequate safety and immunogenicity are demonstrated in the phase 1 studies, vaccines will not be available in substantial quantity until the first quarter of 2015 at the earliest. For that to occur, funding must be secured for production. Even if an effective vaccine can be produced, it is not likely to be 100% effective, so to succeed in stemming the current outbreak, a coordinated effort to improve capacity and provide clinical care in affected countries needs to be scaled up urgently.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

Dr. Kanapathipillai is an editorial fellow at the *Journal*. Other authors are from the World Health Organization, Geneva.

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3. Geisbert TW, Geisbert JB, Leung A, et al. Single-injection vaccine protects nonhuman primates against infection with Marburg virus and three species of Ebola virus. J Virol 2009;83:7296-304.

DOI: 10.1056/NEJMp1412166

Mr. PITTS. I have one more. An article by Andrew von Eschenbach and Paul Howard entitled, "How to Upgrade Ebola Fight."

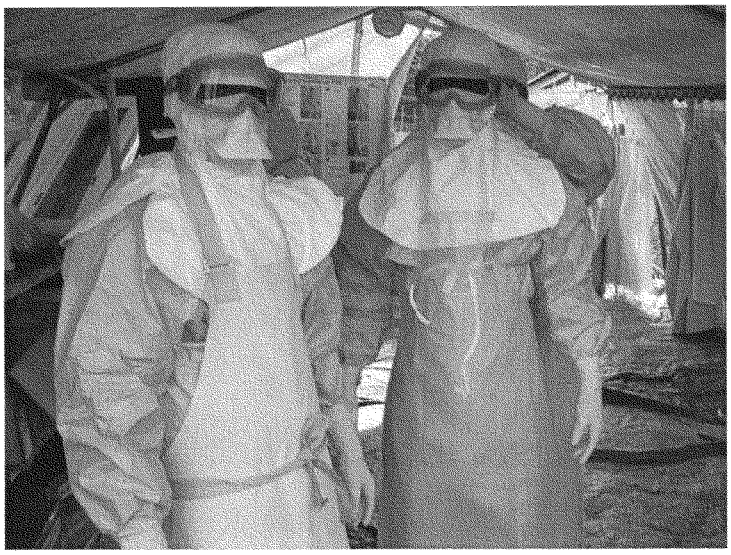
Without objection, so ordered.

[The information follows:]

How to upgrade Ebola fight: Column

Andrew von Eschenbach and Paul Howard 10:08 a.m. EST November 19, 2014

A public-private partnership would increase our chances of developing a vaccine.



Doctors Without Borders in Conakry, Guinea.(Photo: Patrick Fort, AFP/Getty Images)

2 CONNECT 1 TWEETLINKEDINCOMMENTEMAILMORE

Nearly 40 years have passed since Ebola was identified in 1976, but today the United States seems to be caught flat-footed in fighting it. This is despite billions of dollars spent by the federal government after 9/11 preparing for pandemic outbreaks and bioterror attacks.

Why are there are no FDA-approved drugs or vaccines for Ebola? What happened? And going forward, how do we not only win the fight against this virus, but also better prepare for other natural or bioterror outbreaks that could be far more lethal?

We certainly have the technology to beat Ebola. Today, we can map the virus' DNA in days, if not hours, to identify vulnerabilities. Sophisticated diagnostics can measure whether patients are

responding to innovative drugs and vaccines in real time. Industry can churn out promising drugs by genetically modifying plants or animal cells to produce them in bulk. One such promising treatment for Ebola is a trio of monoclonal antibodies called ZMapp, grown in genetically modified tobacco plants.

Vaccines against Ebola have been tested in monkeys since the 1990s, and the U.S., fearful of its potential as a weapon of terrorism, began investing heavily in Ebola research after 9/11. Congress passed Project BioShield in 2004 and reauthorized it in 2013 to finance the development and stockpiling of drugs against the likely agents of bioterrorism – including Ebola.

Congress also created the Biomedical Advanced Research and Development Authority (BARDA) within the Department of Health and Human Services to coordinate multiple agencies, such as the NIH, FDA and CDC, and to streamline government's ability to buy promising drugs and vaccines. Congress even gave the FDA streamlined approval authority for countermeasures based only on animal tests, along with the authority to quickly authorize their use during public health emergencies. Ebola is on BARDA's shortlist.

Why, if we began preparing a decade ago, are we still struggling to catch up?

First, developing a treatment for Ebola is expensive. Small patient populations (often in poor countries) mean limited economic incentives for companies to develop drugs or vaccines. And BARDA's funding is far too small for the many challenges it faces. Drug development is extremely costly – it can easily cost hundreds of millions of dollars to develop a single FDA-approved drug.

Other government agencies, like the Defense Threat Reduction Agency (DTRA), that invested in developing countermeasures for the Pentagon are trapped in government red tape that can slow the process of funding qualified developers. As a recent, and damning, Bloomberg article on America's Ebola efforts noted, "BARDA needs money [and] DTRA can't move quickly."

Putting all of our biodefense chips into the government basket just isn't a winning formula. Government doesn't have the profit-driven culture of rapid testing and innovation, common in the biotech and venture capital sectors, needed to select the best candidates, discard unpromising ones and develop the "winners" quickly.

But if government can't do it alone, what's the alternative?

Congress should authorize a public-private partnership (PPP) designed specifically to mutually fund and develop the most promising drugs and medicines to combat outbreaks like Ebola and bioterrorism.

The partnership, working in close collaboration with the NIH and Department of Defense, would have the authority to invest in a wide portfolio of promising projects, screened by impartial expert advisors. Many would perhaps fail, but with an effective oversight process, the "winners" would be quickly accelerated from discovery, through development, and on to delivery.

BARDA would maintain its role as government purchaser, but would be able to focus on picking from proven products. Our battle against pandemics can also pay dividends in the battle against much more common diseases. Technologies with both defense and civilian applications – like broad-spectrum antibiotics, or antiviral drugs that could be used to treat the flu – could be licensed to biotech or pharma companies at market rates. (Companies participating in the partnership could be given the first opportunity to bid on these products, with licensing revenues ploughed back into development.)

The advantage of a partnership would be that it would be based on a more viable business model, reassuring industry that there would be a predictable market for countermeasures well in advance of public health emergencies. For instance, the Bill and Melinda Gates Foundation's Global Alliance for Vaccines and Immunization (GAVI) helped research, develop, and distribute the first meningitis vaccine specifically for Africa, vaccinating 100 million people and preventing up to 150,000 deaths. In Europe, the Innovative Medicines Initiative brought industry, regulators and researchers together to design better ways of testing treatments for schizophrenia and Alzheimer's; showed that some brain changes associated with autism may be reversible and helped develop a new device for identifying patients at imminent risk of having heart attacks and strokes.

Our battle against pandemics can also pay dividends in the battle against much more common diseases. The partnership should be charged with finding new ways to reduce the time and cost it takes to move innovative new medicines to patients. According to researchers at Tufts University, it can cost more than $1 billion and take 10-15 years to produce a single FDA-approved medicine.

The FDA has made great strides over the past 10 years to become a facilitator of medical product development, but much more can be done, and the partnership would be a great place for FDA to experiment with innovative new approaches like "adaptive licensing" and technologies such as early biomarker qualification that would rapidly accelerate access to life-saving innovative therapies.

The net effect of a nimble partnership is that we could afford to invest in more products and technologies with a much greater likelihood of success, protecting us from biologic threats while also developing better standards for drug development that could benefit patients everywhere.

Thankfully, there's already a bipartisan initiative in Congress – the 21st Century Cures Initiative, led by Michigan Republican Rep. Fred Upton and Colorado Democrat Rep. Diana DeGette -- looking at ways to bring America's drug discovery, development, and delivery framework into the 21st century. Their efforts could pay huge dividends for the fight not only against Ebola, but also for cancer, Alzheimer's and other diseases that threaten us. We have the tools, the technology, the knowhow and the political will to win this fight.

Millions of lives hinge on our success.

Dr. Andrew von Eschenbach is chairman of the Manhattan Institute's Project FDA, and former commissioner of the FDA from 2006 to 2009. Paul Howard is director of the institute's Center for Medical Progress.

Mr. PITTS. I will begin the questioning and recognize myself for 5 minutes for that purpose.

Dr. Robinson, the President's request for emergency Ebola response funding includes $157 million for BARDA for immediate response to manufacture vaccines and therapeutics. The request does not specify or specifically mention if any of these funds would be used for the development of rapid diagnostic tests to identify Ebola. Of the $157 million that was requested in emergency funding, how much do you plan to dedicate for the development of such tests?

Mr. ROBINSON. Thank you for the question, Chairman Pitts. BARDA actually has funds in its ARD program for diagnostics and will be using those funds for development of diagnostics, as many of these diagnostic devices will have applicability not only for Ebola but for other biothreats.

Mr. PITTS. OK. To all the panelists, I understand that HHS has reached out to the private sector, which includes a company from my home State of Pennsylvania, in order to expedite medical countermeasure products. How have companies responded to your request? We will just go down the line. We will start with Dr. Robinson.

Mr. ROBINSON. To date, we have 152 different companies that have come to BARDA and gone through our TechWatch program, telling us about what their product candidates can do and not do. And we have either asked them to submit proposals or directed them to our colleagues at NIH, or even FDA, CDC, and DOD if funding is more directed toward discovery and early development. So we have had a robust response at this point.

Mr. PITTS. Admiral?

Mr. REDD. We receive a number of requests each day, about 20 per week. We generally, for most of those, route them either to BARDA or to NIH or to FDA, depending on the particular issue. Apart from countermeasures, we have had a very vigorous interaction with the private sector on the donation side. It has been very helpful in our response in West Africa.

Mr. PITTS. Dr. Borio?

Ms. BORIO. We have quite a bit of interest from companies. We direct them to the appropriate review divisions to explain the process. We are clearly prioritizing those companies for which NIH, BARDA, and DOD are supporting. We also had quite a bit of interest from the diagnostic industry. We did a lot of outreach for them and to explain the EUA process, and that has also paid off because we have now seen increased interest incoming through the FDA for the development of diagnostic technologies.

Mr. PITTS. Dr. Fauci?

Mr. FAUCI. Very similar, Mr. Chairman, literally a couple per day that get directly referred to us as well as secondary referrals from the FDA or CDC or BARDA when they go to them, and then they send it to us. We have a division in my institute where we have one component of it that essentially spends full time working with industry trying to sort out the things that we can help bring forward for them or things that we might essentially say are not really relevant to what we are doing. Most of them have a positive aspect that we pursue, sometimes immediate, and sometimes it is

going to take a year or so to work it out, but we are very, very closely involved with industry in this.

Mr. PITTS. Thank you.

Dr. Borio, PAHPRA strengthened FDA's current emergency use authority and provided the agency more flexibility to get products to the public in an emergency. I was glad to see the FDA issue an EUA last week for a diagnostic test related to the ongoing Ebola epidemic. Would you please provide more details on the agency's use of these new authorities for Ebola? Are there more tests or therapies that may become available soon to healthcare workers on the front lines?

Ms. BORIO. Well, I can't underscore how important the new authorities have been for us to be able to respond as fast as we have, specifically with the diagnostics. Since the first EUA was issued back in August for the DOD-developed test and that, again, we were able to do that because of these new authorities, and they were critical to be able to put diagnostics in West Africa as well as rapidly deployed within the laboratory response in our work at CDC. We will continue to make use of those authorities as needed.

Mr. PITTS. Is FDA currently examining utilizing trial designs that would ensure that all participants receive the vaccine?

Ms. BORIO. So, Dr. Fauci, would you like to discuss the clinical trial designs for vaccine?

Mr. FAUCI. Yes. We feel very strongly, Mr. Chairman, that in order to definitively determine the safety and efficacy of a vaccine which you will, after all, be giving to normal, healthy people, that you have to have a trial in which not every single person gets the vaccine at the same time because if that is the case, you will never know whether a vaccine works. We are doing a randomized controlled trial in Liberia. The CDC will be doing what is called a step wedge trial in Sierra Leone. I just want to point out to the committee that there were calls back about a month or two ago of distributing the vaccine widely in West Africa without a control group, had we done that, the downturn in Liberia now would have been attributed to the vaccine when, in fact, it was a downturn, and there was no vaccine. So that is the reason why we have got to be careful to make sure we have a control group.

Mr. PITTS. Thank you. My time has expired.

The Chair recognizes the ranking member, Mr. Waxman for 5 minutes of questions.

Mr. WAXMAN. Thank you, Mr. Chairman.

Earlier this month, the administration requested $6.2 billion to enhance the U.S. Government response to the Ebola outbreak. The request included $400 million for NIH, FDA, and BARDA to support the development, manufacture, and testing of Ebola diagnostics, therapeutics, and vaccines.

Dr. Borio, how would FDA use the additional funds in the administration's budget request to advance diagnostics, therapeutics, and vaccines to deal with Ebola?

Ms. BORIO. Well, thank you. So since——

Mr. WAXMAN. Could you speak a little louder or right into the mike?

Ms. BORIO. Sure. So more than 300 FDA staff have been involved in this response, and they represent tremendous scientific expertise

to be able to support this robust pipeline of Ebola products. They have been working full time, all hands on deck, at a very accelerated pace to be able to sustain, and part of the reason why we would be able to respond so rapidly is because of the recent support that this Congress has given us in the last few years through the countermeasures initiative.

Now, to be able to continue to sustain the aggressive response that we think we will need in the foreseeable future, we do need additional resources to hire additional staff so that we can continue doing what we are doing and see the results that we are seeing.

Mr. WAXMAN. Thank you. Dr. Fauci, give us a brief overview of how NIH would use the funds included in the request for your agency.

Mr. FAUCI. Thank you for the question, Mr. Waxman.

The NIH, of the amount that you mentioned, is asking for $238 million. That will be divided into—for example, one big chunk of that is $56 million to conduct the Phase II–III trial, the randomized controlled trial in Liberia, and there is a certain amount to do the secondary and tertiary candidates should that candidate fail, and then there is a chunk of money to go for diagnostics and therapeutics. We have, as Dr. Borio mentioned, a common protocol to test all of the therapeutics that you saw on that list there in one way or another. That takes tens of millions of dollars, to do those kinds of trials. All of that together is the $238 million request from the NIH.

Mr. WAXMAN. I was recently at a conference where people were looking at the ideas for faster cures, getting new therapeutics out to people right away. And they said that if they could eliminate some of those trials that FDA now requires and get their product out faster, it would lower the price and save people's lives. And one person even argued, why not let the individual make the decision how much of a risk they are going to take. How would you respond to that idea?

Mr. FAUCI. I would disagree with that completely, Mr. Waxman, because having had considerable experience in the testing of therapeutic agents and vaccines, I think there is an assumption and an understandable emotional desire when you have a lot of pain and suffering to just give medications to people. There are a couple of things wrong with that. First of all, experience tells us that a substantial proportion of those might turn out to not only be not effective but might actually be toxic. And the thing you learn as a physician on your first day in medical school is, first, do no harm. And despite the dramatic nature of the situation, we really need to determine if they work, and that is the reason why our common protocol allows us to determine whether something is safe and effective.

Mr. WAXMAN. Well, thank you.

To support the clinical trials as well as more widespread use of any therapeutics and vaccines that are proven to safe and effective, we will need to be able to quickly increase their production.

Dr. Robinson, can you discuss how the emergency funding request would help BARDA support expanded manufacturing for promising therapeutics and vaccine candidates.

Mr. ROBINSON. Yes, sir, Mr. Waxman. We are funding, right now, the commercial scale production at NewLink—going forward with that to be able to produce, instead of tens of thousands of doses, hundreds of thousands or even millions of doses going forward. Additionally, with funding that has been requested we would be able to do that with also GlaxoSmithKline and even J&J and Bavarian Nordic.

On the therapeutic side, we certainly are doing that with ZMapp right now by expanding other production facilities and going a different way with what we call CHO mammalian cell production with the other manufacturers and to produce those new antibodies and then be able to have those made at commercial scale so we could have thousands of those treatment courses available immediately.

Mr. WAXMAN. Mr. Chairman, if you will allow me, I wanted to ask Dr. Redd, there is a $621 million for CDC for the domestic response. Can you describe how you plan to use these funds?

Mr. REDD. Yes, sir, thank you. The work would support the ability to improve what we are doing now, identifying cases, getting them to treatment rapidly. So it would provide funding for laboratory development, for improving workforce capacity, improving biosafety, improving hospital infection control, and assuring that personal protective equipment is available for the staff that are providing care to these patients.

Mr. WAXMAN. OK, thank you.

Thank you, Mr. Chairman.

Mr. PITTS. The Chair thanks the gentleman.

Now recognize the vice chair of the full committee, Mrs. Blackburn, 5 minutes for questions.

Mrs. BLACKBURN. Thank you, Mr. Chairman.

And, again, thank you all. This is something we have got to get a handle on, and I think you probably realize from listening to our questions, our constituents are very frustrated with the way that much of this has been approached with the lack of—seeming lack of preparedness that our Federal agencies had, even though they had been hearing about this for months, and then, of course, the fact that our U.S. military, my constituents from the 101st, had to be sent over to build hospitals and to train medical workers. So it is good to hear that you all are engaging the private sector and that you are beginning to work forward on this.

Dr. Fauci, you referenced the slides at the beginning in your testimony. You know, you mentioned the length of time that you all had focused on this, going back to 2001. I would like to encourage you, during that time, time doesn't equal results, basically. And the slow movement of the bureaucracy in preparing to address these category A situations that you outlined is frustrating. And it does show a lack of flexibility. So that flexibility is going to be important going forward, and it is something Congress is going to hold you accountable for.

The private sector moves at a faster pace.

And, Dr. Robinson, I was pleased to hear you say that you are engaging with the private sector as you are seeking a way to move forward with this.

Let me ask you, do you have any, Dr. Robinson, any American pharmaceutical companies that have, in accordance with FDA's IND program, Investigational New Drug Program, sought emergency export provisions and requested recognition from HHS that an emergency situation exists in West Africa that warrants the export of an IND that could be helpful in fighting Ebola?

Mr. ROBINSON. Not to my knowledge, but I would ask my colleague Dr. Borio to help with that.

Ms. BORIO. So this provision has been used to export ZMapp to Liberia, this export provision. And there has been interest expressed by additional companies to export investigational product to Liberia using this export provision, and we are currently working with HHS and the companies to——

Mrs. BLACKBURN. OK. So, Dr. Borio, I am like Mr. Waxman, I can hardly hear you. It is very difficult to hear you here on the dais. So you are saying that only one company, ZMapp, has requested recognition?

Ms. BORIO. No, I am saying that this provision, this export provision has been used by one company, ZMapp, to get the product to Liberia at the request of the Liberian Government.

Mrs. BLACKBURN. OK. So you all have approved only one, and the only one you have approved is ZMapp?

Ms. BORIO. This provision does not—one company has met the requirements for the export provision, and the product was exported to Liberia. We have received interest and questions from additional companies about how to make use of this export provision, and we are working with HHS——

Mrs. BLACKBURN. OK, let me interrupt you then. How long does it take through this to get recognition, for a company to get recognition? Because my understanding is there are other companies that are there, and I do have the letter from the Liberian Ambassador that was dated October 22nd, seeking other options, therapies, and drugs to move forward in this program. So how long will it take you all through this program? Dr. Borio or Dr. Robinson, either one, what is the estimated time that it will take somebody to get through this program?

Ms. BORIO. So for products that are under review at FDA for which we have substantial information already in the product, we are able to move very fast, and we are working hard to resolve the situation for the products for which we have very little information, but our intent is to be able to support export a product when the company is——

Mrs. BLACKBURN. Dr. Borio, I hate to interrupt you again. What we are looking for is a time frame. You know, are you talking about 1 month, 2 months, 6 months? What do you anticipate? How much energy are you going to put into this to save countless lives? How quickly do you think you can move this forward? That is what we are looking for is more of a time frame, please, if you can.

Ms. BORIO. I appreciate the intent of moving investigational product to those countries. I would just—I don't know that to save countless lives—we do not have information on these products' safety and efficacy. Our intent is to support the request of Liberian or West African governments to receive investigational product and

our intent of course is to support companies that are interested in exporting product and——

Mrs. BLACKBURN. I need to interrupt you. My time has expired, but I am going to ask you to please submit in writing a timeline, an orderly process timeline that will give us an idea of how quickly you anticipate these products are going to be able to be available for emergency export.

I yield back.

Ms. BORIO. Thank you.

Mr. PITTS. The Chair thanks the gentlelady.

Now recognize the gentlelady from Florida, Ms. Castor, 5 minutes for questions.

Ms. CASTOR. Thank you, Mr. Chairman.

Thank you all for being here today and for everything you are doing and your teams are doing to combat the Ebola threat and especially containing and stopping the threat from West Africa.

And Dr. Fauci, last time you were here, I mispronounced your name, and I apologize, and I will not do it again.

The ongoing Ebola threat in West Africa is a reminder of the importance of drug and vaccine development when it comes to fighting these viral threats and the keyrole played, our leadership here in America, the key role played by the U.S. Government. While Americans are bombarded by advertisements for various pharmaceuticals because we have an open and competitive marketplace for drugs in America, Ebola is entirely different. Development of therapeutics and vaccines for Ebola and similar diseases is entirely driven by Government activity because the market for these treatments is small and sporadic and because affected countries cannot pay high prices for these drugs, and yet there is a lot at stake. We tend to pay attention to the U.S. Government's role in times of crisis, but we have got to constantly look ahead to foresee potential medical threats long before they appear. So I would like to hear, Dr. Fauci and Dr. Robinson, how do your agencies identify which infectious diseases and biological hazards are top priorities? How do you anticipate what the threats of the future are?

Mr. FAUCI. Well, we can start off by saying that it is impossible to accurately predict what the next outbreak will be. You can have a pretty good idea that looming there in the background is the possibility of there being a pandemic influenza. And that is what we prepare for continually. We are trying to improve our abilities vis-a-vis influenza vaccines, particularly our efforts in trying to develop a universal flu vaccine that you don't have to make every time you get a new strain, as opposed to what we literally have to do every year when we change strains as the virus drifts, and sometimes, with a pandemic, it would shift.

Regarding something like Ebola, which started off in our mind as a threat of bioterror and then, as I mentioned in my opening statement, became a potential threat of a natural emergence because we have seen it emerge 24 times since 1976, The way you prepare for that is to do the kind of research, fundamental basic clinical research, to develop countermeasures.

I might bring up also the question that Ms. Blackburn asked about how long it took to develop an Ebola vaccine. We had been working on that since 2001, 2002, and we were kind of like the lone

wolf on that. We could not get industry even slightly interested in that. So although they can turn out to be quicker than the Government, they did not want to step up to the plate. And it was only just literally a year or so ago that we got the first big company to partner with us, which is the reason why we have a vaccine right now. So we were looking around very aggressively to have partners in industry and could not find one, which is one of the reasons, if not the reason, why we don't have a further advancement on our vaccine effort right now.

Ms. CASTOR. Dr. Robinson?

Mr. ROBINSON. So the other part to that is that the prioritization of biothreats and then other manmade threats is done through the Department of Homeland Security providing material threat assessment determinations, and then the Public Health Emergency Medical Countermeasures Enterprise actually goes through a prioritization—in our Strategy and Implementation Plan that came out in 2012 and is being updated this year—actually goes through that prioritization process. Right now, everything that have been threats are highly there, except the ones that we have actually been able to make medical countermeasures, such as botulinum antitoxins—and to a certain extent with our anthrax and smallpox medical countermeasures—which we have actually been able to make great progress through those. But the others are still there, and they still have all high priority.

As Dr. Fauci said, these product candidates were early in development and as they have progressed, and if we had not had any outbreaks, we would have been picking up normally several of these anyway—but because of that, now we have actually moved forward to help the industry compress the time frame to be able to develop and produce these vaccine candidates and therapeutics from 2 years or 3 years down to a year and a half and maybe even 12 months. And so, by working together, we are actually able to do that with our colleagues at FDA and NIH.

Ms. CASTOR. Thank you.

My time has expired.

Mr. PITTS. The Chair thanks the gentlelady.

Now recognize Dr. Burgess 5 minutes for questions.

Mr. BURGESS. I thank the chairman for the recognition.

Dr. Fauci, let me just take a minute again and thank you for taking care of our nurse, your patient, Nina Pham. It was incredible to watch the press conference and see her conveyed back home to her family that was waiting and just appreciate everything you did to assist her in her recovery.

I mean, I will speak to some of the same frustration you have heard up here this morning, and I so appreciate the fact that there is a vaccine that was on a clinical trial. In fact, I think I was in Mr. Pitts' district for a field hearing in August. And the head of GlaxoSmithKlein was there and talked about literally next week we are going to start this clinical trial. And I am grateful for that. I appreciate the difficulties they have in getting the vaccine to the country because of the technical considerations surrounding the care and feeding of that vaccine and how it has to be stored, but even the acceleration by 1 month of the Phase II clinical trials, going from January to December, with the rapidity with which this

disease is striking down people in Western Africa, I mean, that 1 month could translate into hundreds, if not thousands, of lives, so that is—yes, the country has made a significant investment in getting us all to this point, but we are anxious to move beyond where we are right now because it does seem that we have arrived at this point in history without the tools, and Dr. Fauci, not a criticism, but just a question as far as—and I appreciate your statements on randomized clinical trials, and I realize those are the gold standard under which we all live, but for people who are self-identified as traveling to Western Africa, who voluntarily would like to receive a vaccine prior to going, is there any mechanism for them to be part of those clinical trials?

Mr. FAUCI. The answer is yes because in the Phase I trials, a certain proportion of them have been actual healthcare workers predominantly. I think if you want to get into now the Phase II or III, depending upon whether you are in Sierra Leone or you are in Liberia, if you sign up for a trial, you will be assigned to one or the other of a limb of a trial. If it is a randomized controlled trial, it will be double blind; you won't know what limb you are in. If it is a step wedge, it is a different design that sort of phases in different groups, so there really depends on the trial itself.

I do want to point out, Mr. Burgess, that when you are talking about a vaccine, as you well know from your experience, it is different than a therapy for someone who is sick. When you are dealing with a vaccine, you are dealing with giving it to a normal person, who can do many other things to avoid getting infected in the sense of the personal protective equipment, et cetera. When you are dealing with a therapy for a person who is already sick, that is when you get the compassionate use approach that the FDA has been quite flexible in granting for the therapies.

Mr. BURGESS. Let me just ask a question of anyone on the panel, and maybe the CDC is the best person to ask the question to. How many people—are there any persons currently under treatment in any of the Ebola facilities in this country, or have all those persons been discharged or unfortunately died?

Mr. REDD. I believe, at the current moment, there are no patients in any of the units in the U.S.

Mr. BURGESS. And, Dr. Borio, you remember we had a hearing I was allowed to attend on the Foreign Affairs Committee in September, and the concern came up about a clinical hold on one of the therapeutics that was under development.

Where are we today with releasing that compound from a clinical hold?

Ms. BORIO. Federal law and FDA regulations preclude me from discussing specifics about the product in question. I have asked the company permission to disclose specifics, but the permission was denied.

And but what I can tell you, because it has been reported by the company itself, is that development of product may continue in patients who are infected with Ebola. And to my knowledge, development has not been hampered by the partial clinical hold in healthy volunteers.

Mr. BURGESS. And so that drug is then available for compassionate use in an Ebola patient?

Ms. BORIO. The drug is available for compassionate use in patients with Ebola and for clinical studies in patients with Ebola.

Mr. BURGESS. And how—at the FDA, how are you going about evaluating the risk profile of therapeutics given the high mortality rate of this illness?

Ms. BORIO. So, clearly, it is very important to take into consideration the seriousness of the disease and to be able to properly evaluate the potential benefits and the risks, and that is what our expert reviewers and team of urologists, pharmacologists, our toxicologists will do for every product.

Mr. BURGESS. And I hope you are prepared to share some of that information with us. As time goes by, I think that would be extremely useful.

And, Mr. Chairman, let me just say, of course, we have got the Cures Initiative also going on in the background, and many of the lessons learned with how drug development has occurred or the regulatory effect—or the effects of the regulatory agencies on drug development I think can be instructive for us as we work through the Cures Initiative. So, again, I hope you will be willing to come back and share that information as we go through this process.

Ms. BORIO. It would be my pleasure.

Thank you.

Mr. BURGESS. Thank you, Mr. Chairman.

I yield back.

Mr. PITTS. The Chair thanks the gentleman.

Now recognize the gentleman from Texas, Mr. Green, 5 minutes for questions.

Mr. GREEN. Thank you, Mr. Chairman, and I appreciate you having the hearing today, and I want to thank our witnesses for testifying.

While we are seeing some progress in response to the deadly Ebola virus, much needs to be done in the months ahead to keep Americans safe and develop much needed vaccines and treatments.

Dr. Borio, I want to thank the FDA, because we deal with them—we have dealt with them as long as I have been on this committee. I understand that the FDA has been given—has given 24 hours' notice to some of the Ebola patients that has come into our institutions and on possible, you know, drugs to be able to cure it, and I just appreciate the FDA with that kind of quick response and—because, again, if you are at that level, you know, people will be able to say, "Well, do whatever you can." And I appreciate the FDA; 24 hours is really great, and that is what I have heard from the medical personnel.

You may be aware that a bipartisan group of colleagues and I, Representatives Blackburn, Butterfield, and McCaul, have introduced a bill to allow the FDA to add Ebola to the FDA's Priority Review Voucher Program. This program was authorized in 2007 to promote the development of new treatments and vaccines for neglected tropical diseases. Our legislation would add Ebola to the list of eligible diseases, creating a new tool to advance the development of new treatment and vaccines.

Do you believe that this sort of incentive might encourage further private investment in this effort?

Ms. BORIO. I don't know that it would, but we remain interested in working with Congress and any incentives that may help develop these products. And in the meantime, we will continue to do all we can to provide those incentives, including, for example, we did recently an orphan drug designation for one of the products to—as an incentive. So we think that it is important, clearly, for products such as these to have as many incentives as we can.

Mr. GREEN. Do you know of any other incentives that might be useful in attracting further private sector investment and vaccine research in the development for Ebola or other infectious diseases.

Ms. BORIO. I would be happy to give it some thought and I will get back to you if I——

Mr. GREEN. OK. I appreciate it, and thank you.

Dr. Fauci, in earlier testimony you talked about the linkage between the Ebola drug and vaccine development and the National Institute of Allergy and Infectious Disease. And I am glad our Government and the private sector are stepping up to the challenge of developing vaccines and other treatments for Ebola. I want to make sure we are also paying attention to other tropical diseases that are emerging.

In my City of Houston and elsewhere along the Gulf Coast, we held a 21st Century—I take that back. We held a 21st Century Cures roundtable in Houston recently. Chagas disease is one example of what is known as a neglected tropical disease. It has caused serious heart disease and even death if left untreated. While no one in Houston has contracted Ebola as of yet, several Houston residents have been diagnosed with Chagas, and recently these were not people who had travelled outside the U.S. to places where Chagas is widespread. In the past, NIH has supported regional centers of excellence in emerging infectious diseases, but the neglected tropical diseases were never a significant aspect of that initiative.

Would you be willing to work with me and the committee to find a way to support similar regional centers of excellence in these neglected tropical diseases?

Mr. FAUCI. We certainly would take that into consideration, Mr. Green. In fact, you are referring to my good friend Dr. Peter Hotez, who is there now running that effort with Chagas disease. He was formerly here at GW, and we have had a very close collaboration with him, and I would be more than happy to sit down with you and him and talk about the possibilities in this regard.

Mr. GREEN. Glad to, and I know Dr. Burgess was at that meeting, so was our colleague in the Houston area, Congressman Olson, and be glad to work with you.

Mr. Chairman, that is all the questions I have, and I yield back my time.

Mr. PITTS. The Chair thanks the gentlemen.

Now recognize the gentleman from Pennsylvania, Dr. Murphy, 5 minutes for questions.

Mr. MURPHY. Thank you, Mr. Chairman.

Dr. Fauci, it is my understanding that some enrolled in vaccine trials will be given placebos, of course. Can you discuss any ethical dilemmas this is going to create, and if there is a plan to treat those individuals who may receive the placebo?

Mr. FAUCI. A randomized, controlled, double-blind trial is a classical paradigm for the determination of the safety and efficacy of vaccines. It has gone through the strictest ethical review——

Mr. MURPHY. I understand that. I am just referring to—I don't question that. I just want to make sure that things are in place to monitor closely and treat those who may still show up with systems, either with the vaccine or without the vaccine.

Mr. FAUCI. Absolutely.

Mr. MURPHY. I want to present some of the concerns raised yesterday during the hearing that I chaired in Oversight and Investigations.

When we heard from Ken Isaacs of Samaritan's Purse, the group's doctors and medical aid workers have been in West Africa fighting the outbreak for a long time. He noted, like other health experts, that there is a lot of unknowns with Ebola and, of course, pointed out that, for example, 95 percent of Ebola cases incubate within 3 weeks and then emerge, but as a New England Journal of Medicine article noted, 5 percent may not emerge until some 42 days later.

We have heard there has been some 341 mutations of the virus. This obviously underscores there is a lot we don't know about Ebola, and we need to be humble about that.

So other things Mr. Isaacs raised was that what would happen if this continues to spread; Africa and other portions of India were some of the key features.

Now, in a book that Dr. Frieden recommended I read, "House on Fire," about smallpox, at that time, when they started to use the vaccines, it was also very vigorous on isolation. So much so the way they contained people was they even put guards around the homes of those with smallpox, would not let them travel anywhere, and made sure no one came in contact with them.

So in order to—in moving forward on this, do you see any move forward in terms of dealing with restrictions and containment in the villages in Africa and also travel to the United States as part of this?

Mr. FAUCI. Well, they are two separate issues, Mr. Murphy. One is a patient who is sick with Ebola. Those patients, by routine protocol, go into strict isolation. So that is not a problem.

When you are dealing with an asymptomatic person who you are suspecting might have Ebola, that is a different story. Unlike smallpox, we know that you do not get Ebola unless you come into direct contact with body fluids——

Mr. MURPHY. Not true, because there have been cases where people have been wearing the personal protective gear but have still gotten Ebola. There have been cases where people have been asymptomatic but have had positive tests. There is people who have been symptomatic and have negative Ebola tests. So I want to stop you because you have, in the past, made condescending statements about people who talk about the what-ifs.

Doctor, we are in the business of what-ifs. You are in the business of what-ifs as a clinician, as a scientist, and so are we. We have to ask these questions. And I am deeply, deeply concerned if we continue down this path of arrogance and hubris in saying, "We got this," because we don't.

Because it was also pointed out in "House on Fire," if smallpox came again to the United States, just one case would send people into a panic. We want to help here. And I am pleased that you are moving forward vigorously and the FDA is moving forward vigorously on these vaccine trials, but I also want to make sure that—there is going to be billions of people who don't have the vaccine. And as we are moving forward on this, I want to make sure that we are doing all we can to maintain a high defense perimeter so that people who have been exposed Ebola are not traveling throughout Europe and the United States without other restrictions.

Now, in yesterday's hearing, it almost sounded like, in some ways, that people are spiking the ball that we don't have cases in the United States. But let's face it, we will have more, and I want to make sure that we are following up.

I mean, New York City is saying they want $20 million just to deal with the one case and tracking 500—dealing with 500 people there. So these costs are going to go up.

So a long way of getting to this point, I want to find out, are you going to continue to coordinate the vaccine trials along with other aspects of quarantining, of looking at travel, of dealing with travel issues, so this does not spread to other people who don't have the vaccine?

Mr. FAUCI. The answer is yes. We will do everything within the scientific data that we know, the experience and the realization that there are things that we don't know to do the things that you say.

Mr. MURPHY. Well, with regard to the scientific data, how many cases would it take to overwhelm the system in the United States today?

Mr. FAUCI. I can't give you a number on that, but certainly if we have a major outbreak, the kind that we have——

Mr. MURPHY. We only have, like, 10 bed spaces. Right?

Mr. FAUCI. Well, we are——

Mr. MURPHY. I am not talking about thousands of people getting it. My point is, let's continue to be humble about this. Let's continue to understand there is a lot we don't know and move forward and work as a team on this. We want to help, but I want to just make sure that we are not just telling people, "We got this and everything's fine at this point." We still have a lot we have to learn.

I recognize my time is up, and I yield back.

Mr. PITTS. The Chair thanks the gentleman.

Now recognize the gentleman from New Jersey, Mr. Lance, 5 minutes for questions.

Mr. LANCE. Thank you, Mr. Chairman, and good morning to the distinguished panel.

You have mentioned in your testimony that this is an unprecedented global health crisis, and over the course of the past several months, there has been widespread confusion over hospital best practices, travel protocols, and even treatment options. The distinguished panel sits before the committee today representing four distinct agencies that have been tasked with addressing the crisis. I would ask the members of the panel, how can we ensure that there is no overlap or redundancy in your work?

Dr. Fauci.

Mr. FAUCI. Well, when you talk about overlap, we do have mandates and missions that I believe are synergistic and not overlapping or duplicative, and I tried to explain that on the slide that I showed. If you look at the NIH's responsibilities for the development of concepts, fundamental basic and clinical research to try and understand the disease and the early part of the development of the countermeasures. So you have BARDA, who is involved in the advanced development. You have CDC, whose main mandate is the surveillance and disease control as opposed to the development of countermeasures as we do, and you have the FDA as the regulatory agency. So I think it is a pretty good flow of synergy, as opposed to overlap and duplication.

Mr. LANCE. Others on the panel?

Ms. BORIO. I will just add that we all have our roles, and we work very, very closely together, and we talk several times a week, several times a day sometimes. We have each other on speed dial. So I believe that we are doing everything we can to move in synergy and not duplicate each other's work.

Mr. LANCE. Thank you.

Mr. REDD. I am probably going to say what you have already heard, but I think that the two things are there are specific lanes of effort, but where there are borders or interfaces, we work very closely to make sure that the work we are doing is supportive rather than unnecessarily duplicative.

Mr. LANCE. Thank you.

Dr. Robinson.

Mr. ROBINSON. Yes. I mean, this is not our first time at this. We have done this from H1N1 to H7N9 last year and now this year, and have built up that infrastructureto talk with one another and to actually know what our budgets are and what our strengths are where we can actually tap into one another.

Mr. LANCE. Thank you.

Regarding the point you raised on budgets, has the panel been asked or your agencies been asked to provide information to the administration regarding its recent funding request?

Mr. FAUCI. That is how the budget was developed, actually. We were asked by the administration to make a proposal for what we felt was necessary for us to accomplish our mission to address the Ebola outbreak in West Africa, as well as here potentially in the United States, and each of us submitted a budget proposal, which then ultimately went forth after review at the administration level to the Congress, where we testified a week or so ago to the Senate Appropriations Committee.

Mr. LANCE. Others on the panel, you were involved in the budget request? Others?

Mr. REDD. Yes, along with OMB to coordinate the request through the Department.

Mr. LANCE. Dr. Robinson?

Mr. ROBINSON. Absolutely.

Mr. LANCE. Thank you.

Have you developed action plans specifying how and where the money would be spent if it is approved?

Mr. FAUCI. Yes, sir. When you make a budget proposal, you have to delineate each of the line items. For example, as I mentioned in a response to a question from Mr. Waxman, the NIH request is $238 million. So it just wasn't a bulk request for 238. There was $56 million for the performance of Phase II–III trials. There was $76 million for this and $23 million for that. So they were line item by line item.

Mr. LANCE. And is that true of the other agencies as well?

Ms. BORIO. It is for us.

Mr. REDD. Yes, sir.

Mr. ROBINSON. Absolutely.

Mr. LANCE. Thank you.

I think it is important for the public to know as we move forward in the appropriations process as to how the money will be spent and where the money will be spent. And certainly we want to work together in a cooperative fashion in our oversight role, and I certainly wish all of you well as we overcome this tremendous health challenge, not only to this country but really to the entire world.

Thank you very much, and I yield back the balance of my time.

Mr. PITTS. The Chair thanks the gentleman.

I would like to apologize to the gentlelady from California. I didn't notice you come in.

I would like to recognize the gentlelady from California, Ms. Capps.

Mrs. CAPPS. Thank you, Mr. Chairman.

I want to take one minute to sing the praises of my professional colleagues, nurses, because nurses have really been at the front lines of the Ebola response, both domestically and abroad. And I want to take a moment to highlight their service.

Unfortunately, this also means that some nurses have been infected during their selfless care for other people. The two nurses infected in Dallas highlighted the important concerns about the effectiveness or non-effectiveness of existing training and guidelines for U.S. healthcare workers treating Ebola patients.

I was pleased to see the CDC issue new guidelines October 20th calling for better training and equipment and adopting practices successfully in place now at hospitals at Nebraska Medical Center, Emory, and the NIH. I think we can all agree we wish they had come out sooner. It is critical, however, that the CDC continue to be a leader in setting guidelines to protect our healthcare workers and contain the spread of Ebola.

So, Dr. Redd, since the adoption of the CDC's new guidelines, what has the reaction from hospitals been? Given that guidelines issued by the CDC are voluntary, do you see that hospitals are cooperating in the implementation of these stricter measures?

Mr. REDD. I think the reaction has been extraordinarily positive. That has been seen in the number of people that have participated in training in the use of the new guidelines, in the responses we have gotten from the visits that we have made to hospitals through States to work on hospital preparedness.

I think the one concern is the availability of personal protective equipment, something that we are working on shoring up, but that is probably the major concern.

Mrs. CAPPS. I want to follow up with that topic because I visited two hospitals in my district, and PPE, or the personnel protective equipment, has had such a surge in demand following—and particularly now following your guidelines, in addition to growing demand by other entities worldwide, and what can we do to help with the PPE supply so that—is CDC—and can it ensure the availability of it? Are you working on that?

Mr. REDD. Yes, ma'am. I think there actually are different efforts that have different time horizons. It is—part of our budget request is for personal protective equipment. In the short term, we want to be sure that hospitals that would be treating patients have a supply that is sufficient for a short term——

Mrs. CAPPS. Right.

Mr. REDD And then there is an ability to acquire personal protective equipment from distributors, from the community, and then there is a supply in the Strategic National Stockpile that can shore up. So a layered approach to be sure that there is personal protective equipment available for the care of the patient.

Mrs. CAPPS. And that is—the administration's request for $6.2 billion to enhance the Government's response, is that critical, then, you see to this being able to be carried out?

Mr. REDD. Yes, ma'am. It is a part of that request.

Mrs. CAPPS. Good. And I could—just anecdotally—and the hospitals that I visited in my district corroborate that getting supplies is really high on their minds at that level, as well as the designation of some regional hospitals so that—as you have said, we are going to see more cases, Dr. Fauci, you mentioned. We need to be ready for them.

I wanted to turn to Dr. Borio, and with respect to the FDA, we all, of course, when this outbreak occurs, wish there were more effective treatments and vaccines already available. And we have heard there are several companies at work on such medicines, but they are not yet ready. Your testimony mentioned some of the hurdles that drug developers face. Would you discuss this in a little deeper depth?

Ms. BORIO. So, for these types of products for Ebola, I see two major challenges for developers. One has to do with the fact that the pre-clinical work has to be done—most of it has to be done in high containment BSL–4 laboratories. So, by default, this is going to be a public/private partnership. Nobody can really go at it alone.

And, for subsequent phases, as we are witnessing now with this epidemic, the clinical testing is quite challenging because these outbreaks tend to occur sporadically in unpredictable fashion and in areas of the world where very limited healthcare infrastructure. And that has to be built up a little bit before clinical investigations can take place. So these are pretty two large hurdles for the——

Mrs. CAPPS. Absolutely. I am running out of time, but I wanted to know if you are trying any of the products on people yet? Is there—have we reached that stage?

Ms. BORIO. So we are working with NIH and investigators in Nebraska and Emory to be able to establish the common clinical trial protocol to be able to most effectively and expediently evaluate our safety and efficacy. They are not quite in the phase of clinical in-

vestigations yet. All the use has been done under compassionate use.

Mrs. CAPPS. OK. Thank you.

Mr. PITTS. Chair thanks the gentlelady.

And now recognizes the gentleman from Louisiana, Dr. Cassidy, 5 minutes for questions.

Mr. CASSIDY. This is a great panel. I apologize, as I will ask your questions to be concise, otherwise there is just no hope I will get through my 20 minutes of questions.

Dr. Fauci, it is implied, but not explicitly stated, are the antibodies elicited neutralizing?

Mr. FAUCI. Yes. The antibodies that we——

Mr. CASSIDY. What is the window period between exposure to vaccine of the virus and antibody development?

Mr. FAUCI. Later than usual. It probably takes, I would say, at least 12 days into the course, and maybe 7 or 8 days following the initiation of symptoms before you see good IgM and IgG responses.

Mr. CASSIDY. Now you—and you say good, but is it detectable—good pre-supposes a certain titer, but can you see low titer, perhaps nonprotective, at some point prior to that?

Mr. FAUCI. You do, but it is very, very low, and you don't——

Mr. CASSIDY. OK. I am sorry.

Mr. FAUCI [continuing]. Couple of days.

Mr. CASSIDY. I am sorry. Now, you mention that the only way to determine—and I am all for case control trial—excuse me, for double-blind studies. But it does seem to me having a mortality rate approaching 50 to 90 percent, you can actually differentiate between a downturn because of good infection control and that which is due to vaccination by looking at antibody titers.

If you have less prevalence of disease and there are no antibody markers, it is clearly a case it is infection control. It is not subclinical cases in something which has 50 to 90 percent mortality. Is that a fair statement?

Mr. FAUCI. Right.

Mr. CASSIDY. Now, Dr. Jenner, way back when he did cowpox for smallpox, I am always stuck, did not do a double blind study. He just basically saw he gave cowpox vaccine, and there was less smallpox. There was a mortality rate of 25 percent. So the efficacy was quickly recognized.

Now, knowing that you have plenty of lead-in time to do a case control analysis of a population to see what is the background of certain incidences, it does seem to me that you could do a study which would be single arm or maybe just different doses of vaccine, but which would have a case control, if you will, of a historical control as opposed to one which must be double blind.

Mr. FAUCI. I disagree with you, sir, because if we had done that a couple of months ago, which we were criticized for not doing—why don't we just go out and let the vaccine out following Phase I—if I had done that in September and October, the downturn in Liberia would have bene ascribed to the vaccine.

Mr. CASSIDY. No, you would have looked at antibodies, and you would have seen that there was a decreased prevalence of antibody production.

Mr. FAUCI. With all due respect, sir, you are talking about someone who is infected and has an antibody response. You know they are infected. You don't need an antibody response to tell you that.

Mr. CASSIDY. But let me ask you, is it subclinical cases, or is it the absence of infection that has caused the downtown?

Mr. FAUCI. Downturn in antibodies?

Mr. CASSIDY. You said in Liberia, there is less prevalence of disease.

Mr. FAUCI. Correct.

Mr. CASSIDY. Now, was it subclinical cases, or is it the absence of infection that has caused this——

Mr. FAUCI. I don't know what you mean by subclinical cases.

Mr. CASSIDY. As in people who are exposed to the virus but do not get sick.

Mr. FAUCI. Yes. When you say exposed, do they get infected? There is a difference. You can get exposed and not get infected. If you are infected——

Mr. CASSIDY. If you mean exposed and not infected, then, my gosh, we are actually doing something good there.

I am assuming that there is a—not splitting hairs, but let me just construct it this way. If somebody has exposure to the virus, is infected in some way, but it is subclinical, they will have still have antibody titer.

Mr. FAUCI. Right.

Mr. MURPHY. Now, we can look at a downturn in infection, we know it is either due to less transmissibility and people actually getting infected; it is due to an increased number of subclinical cases; or in the case of a vaccine, it might be that vaccine was protective.

Mr. FAUCI. Right.

Mr. MURPHY. So it seems like the antibody titer would give you clues as to whether or not it is the vaccine giving beneficial effect or whether it is a decrease in infection rate.

Mr. FAUCI. Well, there is one premise that you said that I don't accept, and that is that there are subclinical infections. The——

Mr. CASSIDY. In that case, it makes it simpler, because if there are no subclinical infections, that means that if there is a downturn prevalence of disease, it is either the vaccine or it is infection control.

Mr. FAUCI. It is infection control. There is no doubt in my mind that it is infection control.

Mr. CASSIDY. OK. That is a fair statement.

Now, it does seem as if we could give the immunization in a single arm study, and we could compare it to historical controls.

Mr. FAUCI. But how can you compare it to historical controls if, while you are doing it, the infection rate is going down? You have a changing scene as you are doing the trial.

Mr. CASSIDY. Does the vaccine elicit IgMs?

Mr. FAUCI. It does.

Mr. CASSIDY. Oh, it does?

Mr. FAUCI. It does.

Mr. CASSIDY. OK. And—well, let me revisit that and let me go on to Mr. Robinson.

I am struck by, Dr. Robinson, I am struck by the amount of money that is being requested. And it does seem as if, for example, the CDC is already getting $716 million for global control, global—$416 million for global health, and it is getting $1.3 billion for public health preparedness and responsiveness on the State level. Presumably, this money is over on top that. It seems like the same programs could be repurposed to accomplish this goal. Obviously, we are in a time of fiscal constraint. Is the fiscal constraint—my gosh, this is a lot of money. Why can't we use the money we already have, knowing that we want to do everything we can, but is what we have adequate to do what we need to do?

Mr. ROBINSON. So, with the $157 million that BARDA requested in the President's budget request——

Mr. CASSIDY. I am looking specifically at the global health. That is what I have been before. The global health is getting $416 million now.

Mr. ROBINSON. That is Dr. Redd, not——

Mr. CASSIDY. Yes. I am sorry.

Mr. REDD. Yes, sir. We are using that money. This money would be requested to——

Mr. CASSIDY. I accept that, but you already have money. Can it not be repurposed for that—why do we need additional? Can you not repurpose what you have already received?

Mr. REDD. Well, that money is—let me—I think that it probably is a question that needs to be answered more specifically than I am going to be able to right no in terms of what those funds are being used for now and what the new funds would be used for.

Mr. CASSIDY. Well, how many PPEs are we purchasing?

Mr. REDD. With the funds that we have right now, we have purchased—our aim is to have enough PPE for——

Mr. CASSIDY. But how many is that?

Mr. REDD. It is enough to take care of——

Mr. CASSIDY. Is it a million? Is it 100,000? Is it 60,000?

Mr. REDD. $2.7 million, and that is enough PPE for 250 patient days of care.

Mr. CASSIDY. OK. It seems like a lot.

Mr. REDD. It is expensive.

Mr. CASSIDY. OK. I am out of time. I yield back. Thank you.

Mr. PITTS. Chair thanks the gentleman.

And before I recognize Brett Guthrie, just mention that this morning announcements were made, and our vice chair, Dr. Burgess, will chair the new committee chairman, taking Lee Terry's place. And Brett Guthrie will take his place as vice chairman of the Health Subcommittee. So look forward to working with you.

Mr. Guthrie, you are recognized 5 minutes for questions.

Mr. GUTHRIE. Thank you, Mr. Chairman.

Thank you for those comments, and will enjoy working with you, as well.

Dr. Robinson, I represent central Kentucky. I have Owensboro, which is Kentucky BioProcessing, and I have watched them for quite a while using tobacco plants. Of course, what we are talking about was ZMapps not Kentucky Burley, but using tobacco plants is good. And it is something that we have been real pleased to see develop in our area. And just was there last month with Leader

McConnell to get an update after the ZMapp stories had come forward. And the production of ZMapp through a plant-based process is a little time consuming and led to a recent shortfall of doses. It necessarily wasn't in their plan to have all this out there ready because they were still in trials, but it is my understanding there are currently about 80 doses of ZMapp available and more being produced. And I know that BARDA is working on a final decision—this is my question—on increasing ZMapp production and the final decision is due soon. Do you have an update on that decision of increasing ZMapp production?

Mr. ROBINSON. Yes, sir. Back in September, we actually awarded Mapp Biopharmaceutical, which subcontracted to Kentucky Bioprocess in the production of six campaigns or six lots of ZMapp product. They have finished the first one. I am not sure 80 is exactly the right number, because we actually—it may be a little less than that, but the second campaign is going well, and that is why I reported today that we saw almost a twofold increase in product yield. In the succeeding lots, we think that we will see even more improvement.

Going forward, the funding that we have asked for is actually to help them do more improvements all across the board in the manufacturing process such that they can have more product available sooner.

The product they are making right now that actually has been in the first campaign will be in the first clinical trial studies that the NIH will be doing.

Mr. GUTHRIE. OK. Thanks.

But I—and I would ask that as you make sure that proven, manufacturing processes are considered into all routes of the production, are there other people doing it, and I know this has been a proven manufacturing process, and not put all of our eggs in one basket.

I do want to talk about the funding, and this is—I know it is within your budget. We have an infrastructure capable of developing, testing, and producing medical counter measures with partners. We just discussed ZMapp, which is a positive example of products in the system's pipeline. And I also understand that promising vaccines are being scaled up and will be manufactured commercially.

And what is BARDA's strategy to pay for this? You testified 2015 funds were only sufficient until December of 2014, which is right around the corner, and the commercial production of ZMapp would not be possible in that lifetime. The White House has asked for $6 billion in emergency requests, and only $175 million for BARDA, barely enough for a fraction of these efforts. So can you outline how you are going to scale these manufacturing processes up for these products within that limit?

Mr. ROBINSON. Yes. Well, $157 million was in our request, and we want to thank Congress for providing $58 million already to us in the continuing resolution anomaly. So we already have that money, and we actually have used that, not only for ZMapp, but also to go forward with the development of new Ebola——

Mr. GUTHRIE. Is this new request going to be sufficient to scale up the——

Mr. ROBINSON. Yes. Not only for the therapeutics, but also for the vaccines with the proposals that we actually have in hand with the manufacturers and are negotiating and will be announcing soon.

Mr. GUTHRIE. OK. I am going to ask you one more question, then.

It is my understanding that authority over all BARDA contracts is controlled by the Office of Acquisition Management Contracts and Grants and the Office of the Assistant Secretary of Preparedness and Response.

When we have heard from medical countermeasures, MCM, developers that this cumbersome arrangement has created confusion, unnecessary delays and uncertainty. Regarding the time sensitive review of BARDA's medical countermeasures developing contracts, would you prefer if BARDA was allowed to negotiate, manage, and award its own advance R&D contracts as it has done in the past?

Mr. ROBINSON. So, BARDA originally did actually have the contracting authority. In 2009, the contracting office was moved over to the Office of the Assistant Secretary for Preparedness and Response. Going forward, we would consider any actions that would help expedite the review and execution of these accounts.

Mr. GUTHRIE. My understanding we moved the money back but not the authority. So the statutory authority is still in the other—you would like to have that authority back?

Mr. ROBINSON. We would consider that and many other efforts that go forward. Whatever would work, actually.

Mr. GUTHRIE. But it would speed up development of processes if you did or critical medical countermeasures?

Mr. ROBINSON. It might, but I will say, though, that our contracting shop has done Herculean efforts in a number of different public health emergencies, including H1N1, where they actually moved contracts extremely fast. So I think they are very able.

Mr. GUTHRIE. Well, that was my question. You wouldn't be able to do this without having to have this other step in the process. You think you are capable and able to do that, and you prefer to do it without the other——

Mr. ROBINSON. I think they are capable, and are actually doing that right now with the Ebola epidemics.

Mr. GUTHRIE. Thank you. I appreciate that, and I yield back.

Mr. BURGESS [presiding]. Gentleman yields back.

The Chair recognizes Mr. Griffith, 5 minutes for your questions, please.

Mr. GRIFFITH. I appreciate it, Mr. Chairman.

I did note with some interest just a minute ago Mr. Guthrie mentioned that ZMapp's being grown in a tobacco plant. He said it wasn't the Burley that he grows in his district. My district grows all kinds of tobacco, and if you all need more plants grown, I got a bunch of farmers know how to grow tobacco and can do it very efficiently.

That being said, the Pandemic and All Hazards Preparedness Reauthorization Act requires the FDA to finalize its guidance to industry regarding the development of animal models to support the approval, clearance or licensure of countermeasures. Of course, clarifying how these products may be tested in animals is critical

to developers as human trials are rarely possible. In March of this year, FDA requested an additional 6 months to finalize this guidance.

Dr. Borio, when do you expect this important guidance to be finalized?

Ms. BORIO. It is very important to finalize this guidance. On the bright side, I have to say that the guidance has been well accepted by industry and academics. It is in circulation. We had a lot of consultation prior to putting this guidance together, and we are moving as if this guidance is final, but it is very important, I know, to finalize it. It is a priority for us.

Mr. GRIFFITH. All right. I appreciate that.

Do you have any estimate of time? Six months? A year?

Ms. BORIO. I would like to finalize it as fast as I can.

Mr. GRIFFITH. Yes, ma'am. I appreciate that. Thank you.

Dr. Fauci, I understand that several thousands of Ebola viruses samples cannot be transported to NIH, CDC and other Government labs in the U.S. Because the CDC on behalf of the U.S. Government has not reached agreements with the countries of origin to permit the shipment and research of the samples. I would also note that, on November 5th of this year, Reuters reported U.S. Ebola researchers plead for virus samples.

I would have to assume that the NIH has a strong interest in getting these Ebola virus samples out of West Africa and over to NIH labs and other Government labs. Am I correct in that?

Mr. FAUCI. Yes. It is important for us to get samples to be able to examine them and do the appropriate genomic sequencing.

Mr. GRIFFITH. And that way, you can have a better idea of whether or not it is mutating and how fast it is mutating. Isn't that correct?

Mr. FAUCI. Correct.

Mr. GRIFFITH. And they also would be helpful in creating diagnostic tests. Is that correct?

Mr. FAUCI. Well, certainly you want to match the virus to the diagnostic tests and vice versa.

Mr. GRIFFITH. And likewise, you want samples from as many of the countries affected as you can get, particularly Sierra Leone and Liberia because they may have different strains. Is that correct?

Mr. FAUCI. Well, I am not saying different strains. When you say different strain, that is a big difference. The strain is the Ebola Zaire strain. There may be some slight modifications depending upon mutations, but it is not going to be a different strain.

Mr. GRIFFITH. OK. And I used—that is what happens when you are a country lawyer trying to mess with medical terms, but what you are after is to see if it is mutating and what is going on——

Mr. FAUCI. Correct.

Mr. GRIFFITH [continuing]. Is that correct?

Mr. FAUCI. Correct.

Mr. GRIFFITH. And so if you only get it from one area, you may not be able to see all the mutations that are occurring. Is that accurate?

Mr. FAUCI. You are absolutely correct. You need a wide range of isolates from different places.

Mr. GRIFFITH. All right. And what is the biggest concern about mutations in the Ebola virus? And obviously, I know that, you know, how much more contagious is it is or how much more deadly it is, but what can you tell me about that as well as those obvious ones.

Mr. FAUCI. Yes. From a practical standpoint, something that is feasible is that it could mutate and make the diagnostic tests a little bit less sensitive, or when you make a vaccine that would make a particular response against a virus, it may not be as avidly binding to the virus when you are looking for protection.

There is always out there this issue, is it going to change so much that it dramatically changes its modality of transmission, namely, what you have read about in the newspapers about becoming a respiratory borne virus? Certainly, that is not impossible, but that is a very, very unlikely scenario, simply because in the history of viruses, it really would be unprecedented that a virus, by mutation, would completely change the method by which it is transmitted. So although we always look for that and keep it up as a possibility, it is unlikely. It is more likely that it would have some impact on the accuracy of the diagnostic test.

Mr. GRIFFITH. And let me ask about that, and it is probably too early for you to answer, but is that possibly one of the concerns with the doctor that was recently brought back to Nebraska, that originally the tests indicated he didn't have the disease, and then later it was clear that he did—he was symptomatic when they did the test, but he didn't test positive. Now, I understand there are always errors and mistakes and things happen, but is that one of the concerns that——

Mr. FAUCI. It is, sir, but I think it is something more likely, because we have experienced this before, it is likely that it wasn't that there was anything wrong between the match between the test and the virus but that when he got his first test, his level of virus was so low in his body that the test wasn't sensitive enough to pick it up. And when you wait a couple of days the way they did, they got a positive test. So there was no problem with the diagnostic test. It was likely that his level of virus was doing this and then started to go up. So when they did the first test, it might have been quite low, and then when they did it a few days later, it was high enough to pick up.

Mr. GRIFFITH. And how many days was it, because I thought I had read somewhere that it may have been close to a week.

It was 4 days.

Mr. FAUCI. Four days.

Mr. GRIFFITH. All right. I see my time is up, and I appreciate your answers.

And I yield back.

Mr. BURGESS. Gentleman yields back.

At this time the Chair now recognizes the gentlelady from North Carolina, 5 minutes for questions, please.

Mrs. ELLMERS. Thank you, Mr. Chairman.

And thank you to our panel for being here on this issue. I know we are all very motivated to move forward on treatments and cures, vaccines for Ebola and certainly so many other diseases.

And I just want to say right off the bat that I had the pleasure of hosting a 21st Century Cures Initiative roundtable discussion in my district. Dr. Robinson was kind enough to come to it and attend. It was very well attended. It was wonderful information that we accrued, and it basically all had to do with vaccines. It was right about the time that the Ebola situation was really starting to come to the forefront, so it has now become so timely.

I do want to start off by asking Dr. Robinson a question, and this gets back to the funding request of $157 million. I just want to make sure that we all understand the process.

When the initial trials are being run and when there is a drug that is being investigated, looked at for success, it is still in the NIH space. Is that correct?

Mr. ROBINSON. So NIH will fund a preclinical study, and then the transition in the Phase I studies is when NIH funds that, and then we go with the subsequent studies afterwards.

In parallel to that, though, there is the development of the vaccine, the vaccine manufacturing process, the analytical tools—actually being able to lot release the vaccine and to be able to do the subsequent Phase II and Phase III——

Mrs. ELLMERS. So there is a little bit of a simultaneous—you know, between BARDA and——

Mr. ROBINSON. We hand off, actually, and I can give you other examples with other vaccines, which—we actually do this, where we actually handle the manufacturing, and the NIH handles the Phase 1 clinical studies. Again, looking at our strengths, so that then it is a seamless transition as it goes forward.

Mrs. ELLMERS. And I guess that is the question. What I am looking for is, I want to make sure that there isn't necessarily a clear stopping point and then BARDA comes in so that we can actually be moving forward.

So, keeping in mind the funding request, how many vaccine candidates do you believe BARDA will be able to support when we look at this? And I know we have been talking about a few numbers, but if you could give us a——

Mr. ROBINSON. So, with the funding request that we have, we will be able to provide funding for four vaccine candidates of the five that NIH has and DOD have supported previously.

Mrs. ELLMERS. OK. So four——

Mr. ROBINSON. Four of the five.

Mrs. ELLMERS. Four of the five. OK. And then to the question, too—and, there again, this is just me trying to understand the process. So, from that point on, will HHS be the purchaser of the Ebola vaccine?

Mr. ROBINSON. So at such time that a decision has been made, when we know that the vaccine has been well tolerated, that the vaccine works, and that there is real need to do so, then HHS will be certainly one of the purchasers of the vaccine. There will be others, including GAVI, that will actually mobilize the overall global effort to purchase vaccines.

Mrs. ELLMERS. OK. Thank you.

Dr. Fauci, I would like to ask a little bit about some of the public-private partnerships that NIH and the private sector have been

undergoing with the Ebola vaccine, especially when we are talking about the medical countermeasures against the threat.

Can you describe to us the National Institute of Allergy and Infectious Disease moving forward? What can we do a better job working with BARDA, that the National Institute of Allergy and Infectious Disease can work better with BARDA? Is there something that we can do to move that process forward in a more efficient manner?

Mr. FAUCI. Yes, Mrs. Ellmers, I don't think so. We work pretty well, not only on Ebola—as Robin said, we have done this movie before. We did it with pandemic flus. We did it with regular flus. We did it with MERS and SARS, et cetera. So we have a long history of working pretty well interdigitating between ourselves and BARDA.

Mrs. ELLMERS. Great. So you feel very confident in the process as it is right now, then, as far as that?

Mr. FAUCI. Well, we always can do better.

Mrs. ELLMERS. Right.

Mr. FAUCI. I don't want to go on the record for that, but I can tell you that I feel pretty good about how the interaction between BARDA and FDA and ourselves has gone.

Mrs. ELLMERS. Working very well.

Mr. FAUCI. And the CDC, because they are involved in the front end with it.

Mrs. ELLMERS. Right. Exactly.

OK. I have just a moment. Well, I will tell you what. I am just going to stop there because I think my line of questioning would be too lengthy, and, again, I just want to say thank you all of you for being here on this issue.

Mr. BURGESS. Gentlelady yields back her time.

The Chair recognizes the gentleman from Florida, Mr. Bilirakis, 5 minutes for your questions, please.

Mr. BILIRAKIS. Thank you, Mr. Chairman. I appreciate it very much.

And I appreciate the testimony by the panel today, and I have a couple questions.

I recently held a roundtable in my district to discuss Ebola with local officials and first responders. I wanted to see if they received the training and resources available to adequately diagnosis and, of course, treat any infected patients.

During the roundtable, a few questions came up, and I wonder if I can get a response.

Admiral Redd, I was told the CDC had only designated one lab in Florida. I represent the Tampa Bay area, and the lab, apparently, is located in Miami to verify possible cases of Ebola. They were concerned that this might be impractical since it is impossible to transfer potentially infected blood by mail. Will more labs be allowed to verify cases specifically in my State of Florida, and why was Miami chosen?

Mr. REDD. So thank you for the question.

The laboratories that are—that CDC works with to do the reference diagnostic test for Ebola are part of the Laboratory Response Network. So those laboratories have training in a wide vari-

ety of diseases, and so that is the group that CDC has worked with.

As far as transport, in general, that is handled by courier rather than mail to get the specimens as quickly as possible to a laboratory that can do the test that has all of the quality control and the sensitivity that is necessary.

Mr. BILIRAKIS. So there are no other labs that qualify in this instance in the State of Florida?

Mr. REDD. I am not sure if there is another Laboratory Response Network laboratory in Florida. I could get back——

Mr. BILIRAKIS. Can you please get back to me on that?

Mr. REDD. In general, the State health laboratory——

Mr. BILIRAKIS. It is a huge State, as you know.

Mr. REDD. Yes, do that test, and so there are a limited number in the country, as you noted.

Mr. BILIRAKIS. Thank you.

This is for the panel. President Clinton and President Bush both had a special assistant for biodefense on the National Security Counsel. That individual ran an annual simulation for pandemic influenza and graded agency performances. I was an original cosponsor of legislation in a previous Congress to create a permanent special assistant position.

Would a permanent special assistant position for biodefense allow for better coordination in planning for future outbreaks, and for the panel?

Mr. REDD. I think the system that we have in place now is working very well. So I think that would be my personal recommendation. I don't think we have a policy on that.

Mr. BILIRAKIS. Do we have a clear figure in command?

Admiral REDD. Mr. Klain is the coordinator across all of the Government for the response. He works on the policy issues and is really helping to identify the things that need to be done and make sure they get done as quickly as possible.

Mr. BILIRAKIS. Does anyone else want to give their opinion on that?

Mr. FAUCI. If you exclude Ebola and talk about just how we handle things in general, and then I will mention, as Steve did, about the current Ebola response coordinator, the ultimate responsibility for that is in Homeland Security. So the Homeland Security advisor, Lisa Monaco, and that is the reason why, early on in the epidemic, when we were talking about the White House coordination, it was with Lisa Monaco. Then when it became clear that this was a full-time job, that she had other responsibilities, and that is the reason why we then brought in Ron Klain, who is the Ebola response coordinator, because this became a full-time job, and—but, in general, prior to Ebola and likely after Ebola, it will still stay at the level of the Homeland Security.

Mr. BILIRAKIS. OK. Next question for the panel, again, is there a national biodefense plan for future outbreaks? Who would like to respond first?

Mr. FAUCI. It is part of the second slide that I showed was the bio defense agenda still holds true, and it involves multiple agency. It involves ASPR, which includes BARDA, FDA, CDC, and NIH, and that is just for HHS. We also have collaborations with the De-

partment of Defense and the Department of Homeland Security. So that was developed soon after 9/11, and that agenda still holds true.

Mr. BILIRAKIS. So there is a plan in place?

Mr. FAUCI. Yes.

Mr. BILIRAKIS. Anyone else want to comment on that?

Mr. ROBINSON. So the National Health Security Strategy is being updated—I think it is every 2 years—but that has already been put into place, and that is where we actually—these action plans can fall down from or cascade down from.

Mr. BILIRAKIS. OK. Thank you very much.

I guess my time—I have got about 4 seconds. I will yield back. Thank you.

Mr. BURGESS. Gentleman yields back his time.

I am just going to ask a couple follow-up questions. I ask unanimous consent to do that.

Without objection, so ordered.

Dr. Fauci, that was a fascinating exchange between you and Dr. Cassidy, and I actually enjoyed that very much. It was one of the most instructive 90 seconds that I have seen on this committee in the 10 years that I have been here.

But it did raise a question in my mind. It is pretty much—well, not—shouldn't say that, but the use of convalescent serum, for example, in Brantly's case, hard to know whether that was what really helped or not, but it seems to be attractive enough that it is continuing to be used, but does the use of convalescent serum in any way cloud the antibody picture that then you have to look at when you are reconstructing responses to this illness?

Mr. FAUCI. The answer is no. It doesn't cloud it, because the circumstances, Mr. Burgess, that you would use convalescent serum is someone who is sick and you are trying to bring the level of virus down. So it doesn't matter if it clouds the ongoing endogenous IgM and IgG response to the person. That becomes almost irrelevant because it is clear that that response may not be adequate to suppress the virus without help. So the convalescent serum is from someone who has already hopefully peaked.

Now, one of the problems that we are facing in evaluating convalescent serum is that it isn't a static level of antibody. It goes up, and it comes down. So if you transfuse convalescent serum late in the game, you may not have very good tiers. So one of the things we are trying to do in the broad study of convalescent serum is to make sure we titrate it and know exactly what we are giving to someone, as opposed to guessing that this person might having a high titer and this person might have a low titer. So that is one of the questions that we are addressing.

Mr. BURGESS. So you are attempting to quantify it?

Mr. FAUCI. Yes. Exactly.

Mr. BURGESS. And then, Dr. Borio, does that require compassionate use? Does the FDA need to give approval for the use of convalescent serum?

Ms. BORIO. So, today, the use of convalescent serum in the U.S. has been done under compassionate use.

Mr. BURGESS. So all of those cases that have been treated in the United States hospitals have been compassionate use?

Ms. BORIO. Yes. And I just wanted 2 seconds with regard to—you know, there are major questions about the benefit of convalescent plasma, and, again, it just underscores the importance of doing proper clinical investigations because we do not want to come into the next outbreak, you know, with the same questions we have today about the benefit of convalescent plasma because it is a laborious type of therapeutic to administer.

Mr. BURGESS. Let me just ask you, and this, of course, is something that weighs heavily on my mind, having been in north Texas when the outbreak occurred. I mean, I share everyone else's concern about travel and restrictions, but what really keeps me up at night is that unknown person who is going to walk in the back door of an emergency room in any of our communities across the country, and the entire cascade of events that happened in Dallas could be revisited.

Do you think we are any better prepared, or have we informed people? Do you think there is better awareness, or are we still just as vulnerable as we were on September 25th?

Dr. Fauci. Yes, sir.

Mr. FAUCI. I think there is a big difference now. The awareness of the importance of a travel history, I think, should have been embedded, but certainly now is embedded in everyone's mind so that if someone comes into even the smallest facility with symptoms that are suggestive of Ebola, it is almost instinctive now that you are going to ask, "Have you had any recent travel, wherever that may be?" If they say "West Africa," a big red flag goes up, and that is why the CDC right now, working with the State and local health authorities, are trying to say that not every hospital in the United States should be able to take care intensively of an Ebola patient, but you should at least be able to recognize and temporarily isolate them until you get the proper transportation to a facility that can. So I think, Dr. Burgess, that we are very, very different than we were a couple of months ago.

Mr. BURGESS. Yes. I just hope we don't have short memories.

Mr. FAUCI. Yes.

Mr. BURGESS. Let me just ask for the entire panel, is there any development in your agencies in the past week that you would like to highlight or note as this committee concludes?

Mr. REDD. Yes, I am actually going to answer the previous question that one thing that we have done also——

Mr. BURGESS. Yes.

Mr. REDD [continuing]. To make sure that that situation that you described doesn't happen is track all of the individuals who travel from West Africa so that if a person does develop symptoms, they are in touch with the health department, with CDC, and we can route them to a place where they will get the kind of care that they need. That is not really the last week, but that is something that is getting better and better.

Mr. BURGESS. And that is a 24-hour-a-day contact that they have available to them?

Mr. REDD. Yes, sir.

Mr. BURGESS. Dr. Robinson?

Mr. ROBINSON. It may seem like a small milestone, but it is a big one for us because our Fill Finish Manufacturing Network that

was only set up 2 years ago—actually yesterday we awarded a task order, the first task order to actually put ZMapp into vials—and so over the next couple of weeks, the bulk product will be going from Kentucky to Indiana and to Nanotherapeutics and Baxter, and they will be filling it into the proper containers and making it available then to the NIH to do the first clinical studies in January. So, for us, it actually shows it is happening right now.

Mr. BURGESS. Yes, that is big news. I appreciate you sharing that with the subcommittee.

Oh, sorry, Dr. Fauci?

Mr. FAUCI. Just one comment, Dr. Burgess, that I would like to make because it has come up several times in the hearing, and in fact Mr. Murphy had said that sometimes when I, he heard that when I respond to a question like this, I do it in a condescending way. It isn't so. We are very sensitive to the situation that is going on right now in Africa. And we want to do two things: no harm and help people. And that is what drives the need to do the kinds of trials that, in fact, may seem to some to be insensitive because they have a control arm, but I have to tell you from decades of experience of things that have gone wrong when you don't get the right answer, it is not because we are insensitive and it is not because we are arrogant. We really feel very strongly that we want to help people and, on the way, not hurt people, and that is very important. So I just wanted to make sure—he isn't here, I wanted to get it on the record so that——

Mr. BURGESS. I appreciate you sharing that with us, and I did recognize that you had wanted to say something, and we moved on on the panel, and I actually thank you for bringing that to our attention. That is a very important point.

And we on this subcommittee do appreciate your service at the NIH. It is something the country would be at a loss without.

And thank all of you for sharing with us today. I remind members they have 10 business days to submit questions for the record. I ask the witnesses to respond to the questions promptly. Members should submit their question by the close of business on Friday, December 5th.

Without objection, the subcommittee is adjourned.

[Whereupon, at 12:31 p.m., the subcommittee was adjourned.]

[Material submitted for inclusion in the record follows:]

PREPARED STATEMENT OF HON. FRED UPTON

Today the committee is holding its third hearing on the Ebola epidemic in West Africa. This is a global threat, and we need to work together—Congress, government agencies, and product developers—to successfully combat this epidemic. Today we focus on medical product development, including treatments, vaccines, and diagnostics, related to Ebola. We'd like to get a better understanding of where we are in the development of these products and what more we need to do to help treat those who are sick, prevent further spread, and prevent another outbreak in the future.

We will hear from experts from the Food and Drug Administration, National Institutes of Health, Centers for Disease Control and Prevention, and Biomedical Advanced Research and Development Authority about how these agencies are working with product sponsors on the design and operation of clinical trials, manufacturing, and distribution.

We will also examine how various Government agencies are working together to ensure that products are developed and deployed as quickly and safely as possible.

Finally, we'd like to hear more from the agencies on how they plan to utilize existing products and help with the development of new products both here and abroad.

In 2013, Congress enacted the Pandemic and All Hazards Preparedness Reauthorization Act in an effort to ensure that we are prepared to respond to an epidemic—just like the very situation we are confronted with today. The law authorizes funding for the purchase of medical countermeasures and increased support for advanced research and development of potential medical countermeasures, and it requires more coordination and prioritization among the agencies represented today in product development.

As we continue to evaluate our response to the ongoing Ebola outbreak, it is important that we understand how that law has helped in responding to this epidemic and if there are areas Congress may need to reevaluate. Our work will continue to ensure we are doing whatever it takes to keep Americans safe.

I appreciate all of you being here today to testify on this important issue.

Congress of the United States
Washington, DC 20515

January 8, 2015

Dr. Anthony Fauci
Director
National Institute of Allergy and Infectious Diseases
National Institutes of Health
9000 Rockville Pike
Bethesda, MD 20892

Dear Dr. Fauci:

Thank you for appearing before the Subcommittee on Health on Wednesday, November 19, 2014, to testify at the hearing entitled "Examining Medical Product Development in the Wake of the Ebola Epidemic."

Pursuant to the Rules of the Committee on Energy and Commerce, the hearing record remains open for ten business days to permit Members to submit additional questions for the record, which are attached. The format of your responses to these questions should be as follows: (1) the name of the Member whose question you are addressing, (2) the complete text of the question you are addressing in bold, and (3) your answer to that question in plain text.

To facilitate the printing of the hearing record, please respond to these questions with a transmittal letter by the close of business on Thursday, January 22, 2015. Your responses should be mailed to Adrianna Simonelli, Legislative Clerk, Committee on Energy and Commerce, 2125 Rayburn House Office Building, Washington, D.C. 20515 and e-mailed in Word format to **Adrianna.Simonelli@mail.house.gov**.

Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely,

Joseph R. Pitts
Chairman
Subcommittee on Health

cc: The Honorable Frank Pallone, Jr., Ranking Member, Subcommittee on Health

Attachment

Questions for the Record

House Energy and Commerce Committee, Subcommittee on Health

Nov. 19, 2014, Hearing: "Examining Medical Product Development in the Wake of the Ebola Epidemic"

Dr. Anthony Fauci, Director, NIAID

NOTE: CONTENT ACCURATE AS OF JANUARY 20, 2015

The Honorable Joseph R. Pitts

1. **As you know, there is an important public-private partnership that takes place between NIH/NIAID and the private sector with ongoing Ebola vaccine and drug research, as well as MCMs against other threats.**
   a. **Please describe the importance of this partnership.**
   b. **Please describe how the research at NIAID eventually moves to advanced development projects at BARDA?**
   c. **Would you say this process has been successful? How could it be improved?**

NIAID Response: Partnerships with industry are critical in NIAID's efforts to develop therapeutic and vaccine candidates for Ebola and other emerging and re-emerging infectious diseases. In this endeavor, it is important to have as many vaccine and therapeutic candidates as possible because candidates that showed early promise may not proceed successfully through the entire development pipeline. To this end, NIAID collaborates with the private sector, including small businesses, academic researchers, and biotechnology and pharmaceutical companies, to identify, develop, and evaluate promising medical countermeasures (MCMs).

For example, partnerships between NIAID and industry have facilitated the Phase I clinical testing of Ebola vaccine candidates. NIAID advanced one of these candidates, cAd3, in partnership with the pharmaceutical company GlaxoSmithKline (GSK). NIAID is conducting Phase I trials of this candidate and an additional vaccine candidate, rVSV-EBOV, developed by the Public Health Agency of Canada and licensed to NewLink Genetics Corp. In collaboration with GSK, the Department of Defense (DOD), the Government of Liberia, and NewLink, plans are underway to move these vaccine candidates into Phase II/III efficacy testing, including in West Africa.

In addition to Ebola vaccine candidates currently in clinical trials, NIAID has partnered with universities and biotechnology and pharmaceutical companies to support a number of Ebola virus vaccine candidates in various stages of development. NIAID also supports research on MCMs by providing preclinical services such as animal testing to researchers. These resources are designed to assist academic and industry partners in advancing their products along the development pipeline. For example, NIAID's preclinical services have been used by private

partners to evaluate more than 30 different filovirus vaccine formulations since 2011. Several of these candidates qualified for further testing, and a number are currently undergoing further development by private industry; Johnson & Johnson recently began a Phase I trial of an Ebola vaccine candidate developed with NIAID preclinical services and direct support.

In the development of all MCMs for biodefense and emerging and re-emerging infectious diseases, NIAID coordinates with multiple partners to translate scientific discoveries into safe and effective MCMs. If candidate MCMs show promise in animal studies or early human testing, NIAID transitions these candidates to the Biomedical Advanced Research and Development Authority (BARDA) for advanced development. This process has worked well to advance development of a number of important MCMs; examples of recent successful transitions from NIAID to BARDA include vaccines and therapies for anthrax, smallpox, and pandemic influenza, including two smallpox antiviral drugs, and a next-generation treatment for chemical exposure. NIAID works closely with BARDA to continually assess the transition process and incorporate lessons learned from previous successful transitions.

In partnership with BARDA and others, NIAID is working to accelerate the development of MCMs for Ebola virus to respond to the current outbreak in West Africa. NIAID is partnering with DOD and BARDA to advance the development and testing of the Ebola therapeutic candidate ZMapp. ZMapp, developed by Mapp Biopharmaceutical, Inc., with support from NIAID and DOD, is a combination of three antibodies that has been shown to protect monkeys from death due to Ebola virus. NIAID's preclinical services are being used to provide preliminary safety data to support the use of ZMapp for clinical trials in humans. BARDA is working with Mapp Biopharmaceutical to accelerate the manufacturing of more ZMapp so that clinical safety and efficacy testing can begin as soon as possible. BARDA is supporting the large scale production of the NIAID/GSK and NewLink Ebola vaccine candidates for potential mass vaccination campaigns.

NIAID's longstanding and successful collaborations with BARDA and other partners are critical to the development of treatments and vaccines for Ebola virus disease. As additional MCMs show promise in early-stage testing, NIAID will continue to coordinate closely with BARDA to transition these candidates for advanced development.

2. **Please provide the Committee with an overview of the Ebola vaccine candidates that are on the horizon and where they are in the process of moving into clinical trials and eventual mass vaccination campaigns in West Africa. As I understand it, your Institute has been funding the development of not only a monovalent Ebola vaccine, but also a multivalent Ebola/Marburg vaccine.**

NIAID Response: A safe and effective Ebola vaccine could be a critically important tool to help prevent Ebola virus disease and help contain future outbreaks. The hope is that such a vaccine could be licensed and used in the field to protect frontline healthcare workers and individuals living in areas where Ebola viruses exist. NIAID has worked to advance a number of Ebola

vaccine candidates into clinical testing to determine if they are safe and effective in preventing Ebola virus disease.

NIAID is currently testing or collaborating with partners to test Ebola vaccine candidates in Phase I/Ib clinical trials in the United States, Europe, and Africa, with plans to move promising candidates into Phase II/III efficacy testing, including in West Africa. NIAID, in partnership with GlaxoSmithKline (GSK), developed two versions of the chimp adenovirus-vectored cAd3 Ebola vaccine. The first is a bivalent cAd3 vaccine that contains genes from two Ebola virus species, including the Zaire Ebola virus responsible for the current outbreak in West Africa. A small Phase I study to examine the safety and ability of this candidate to induce an immune response in humans began on September 2, 2014, at the NIH Clinical Center in Bethesda, Maryland. Initial results from this trial indicated the vaccine is well-tolerated and produced immune system responses in all 20 healthy adults who received it. The second version of the cAd3 vaccine is a monovalent vaccine including just a single Zaire Ebola virus gene. The monovalent cAd3 vaccine is undergoing testing by NIAID as well as by collaborators in the United Kingdom and the West African country of Mali. In October 2014, GSK and World Health Organization partners began an additional, larger clinical study of the monovalent vaccine in Lausanne, Switzerland. A booster vaccination designed to follow the cAd3 vaccination and induce a more durable response is being developed. The booster vaccine, a modified Vaccinia virus Ankara (MVA) including a gene from the Zaire Ebola virus, is scheduled to enter Phase I testing in 2015. In addition, NIAID and the Department of Defense (DOD) are conducting Phase I trials of another vaccine candidate, a recombinant vesicular stomatitis virus (rVSV)-vectored Ebola vaccine, in development by NewLink Genetics Corp. In partnership with GSK, DOD, the Government of Liberia, and NewLink, plans are underway to advance the cAd3 and rVSV-vectored Ebola vaccines to Phase II/III efficacy testing, including in West Africa.

In addition to vaccine candidates in Phase I trials, NIAID has supported a number of Ebola virus vaccine candidates along the product development pipeline. NIAID is supporting the biotechnology company Profectus BioSciences, Inc., to develop a multivalent rVSV-vectored vaccine candidate against Ebola and Marburg viruses. The Profectus BioSciences' monovalent Ebola vaccine has transitioned from NIAID to BARDA for advanced development. NIAID also is supporting the biopharmaceutical company Crucell in their development of a multivalent Ebola/Marburg vaccine using recombinant adenovirus vector platforms. NIAID played an instrumental role in the collaboration between Johnson & Johnson (parent company of Crucell) and Bavarian Nordic on a two-dose (prime-boost) vaccination regimen. Crucell contributed its multivalent Ebola/Marburg vaccine and Bavarian Nordic contributed its MVA-vectored vaccine for the two-dose vaccination regimen that began Phase I testing in early 2015.

NIAID intramural scientists are collaborating with academic researchers and have produced two Ebola vaccines that have been shown safe and protective in monkeys. Clinical lots of the two vaccines are currently being manufactured, and Phase I trials are planned for mid-2015. The first, an inactivated vaccine with the glycoprotein from Zaire Ebola virus expressed in a recombinant rabies vaccine construct, provides protection against rabies and Ebola virus disease in monkeys. This candidate was recently licensed to Exxell BIO of St. Paul, Minnesota, which aims to

advance the product through clinical testing and potential commercialization. The second vaccine, which is a live attenuated vaccine targeted against Zaire Ebola virus, is distinctive as it will be administered as a nasal (mucosal) immunization.

3. **What initiatives are underway at the Department of Health and Human Services (HHS) to improve care for patients who are infected with Ebola today?**

NIAID Response: The National Institutes of Health has developed and will implement a randomized, controlled trial to examine a variety of potential therapeutic interventions for Ebola virus disease. The first intervention to be tested is the monoclonal antibody cocktail known as ZMapp. The study will be conducted simultaneously in the United States and Liberia, with possible extension to other countries in West Africa.

4. **Given many of the well-reported supply challenges with mass-producing and manufacturing Ebola drug treatments, such as ZMapp and others, in the near-term pipeline of Ebola experimental and investigational treatments, do you see potential options that could have the drug supply available to actually treat thousands of Ebola patients in West Africa?**

NIAID Response: NIAID is committed to working with our partners to evaluate candidate Ebola treatments and vaccines for safety and efficacy. At this point in the outbreak, we are still working to generate the evidence to show whether potential interventions are safe and effective by moving these products expeditiously along the development pipeline into clinical trials. The data from the current and planned Phase I trials will help demonstrate whether candidate Ebola vaccines and therapeutics are safe and show signs of potential efficacy. Successful candidates will be advanced to efficacy testing in larger numbers of people in West Africa. As we proceed through clinical testing, we will continue to work with our partners in the Food and Drug Administration to advance these studies as safely and quickly as possible. We will continue our longstanding and successful collaboration with the Biomedical Advanced Research and Development Authority (BARDA) to transition candidate Ebola therapeutics and vaccines for advanced development. As mentioned in the response to question 1, BARDA is supporting manufacturing activities for ZMapp in tobacco plants to make sure that the product candidate is available in sufficient quantities for upcoming clinical trials in West Africa. BARDA's Fill/Finish Manufacturing Network is filling the ZMapp product for clinical studies. Additionally, BARDA engaged other tobacco-based biopharmaceutical companies to produce ZMapp. Lastly, BARDA partnered with Genentech and Regeneron to develop and manufacture ZMapp and new Ebola monoclonal antibodies using specialized Chinese hamster ovary (CHO) cells. These CHO cell-derived monoclonal antibodies are currently being evaluated in nonhuman primate challenge studies against Ebola and, if promising, may enter clinical trials in West Africa soon. If successful in those studies, doses of the monoclonal antibodies will be manufactured at

commercial scale at these companies and the Centers for Innovation in Advanced Development and Manufacturing (CIADMs), resulting in thousands of treatment courses later in 2015.

5. **What is the role and pathway to join the global coalition of clinical trials for finding effective new experimental therapies in patients with Ebola Virus Disease in West Africa?**

NIAID Response: Global coordination and cooperation will be crucial to finding safe and effective therapies to treat Ebola virus disease. The National Institutes of Health (NIH) is collaborating with industry partners, Ministries of Health in affected countries, and others to advance clinical trials of experimental therapies for Ebola virus disease such as ZMapp. Ministries of Health interested in being part of the NIH studies are encouraged to make a formal request to the U.S. Department of Health and Human Services.

6. **How would a treatment that focused on surviving the deadly complications of Ebola rather than the virus itself be tested in the coalition forming for clinical trials in West Africa?**

NIAID Response: Treatments focused on surviving the complications of Ebola would have the same endpoint as treatments focused on the virus, namely whether the treatment improves survival of individuals with Ebola virus disease. The National Institutes of Health has developed and will implement a randomized, controlled trial to examine a variety of potential therapeutic interventions for Ebola virus disease. The study will be conducted simultaneously in the United States and Liberia, with possible extension to other countries in West Africa.

7. **For experimental treatments that are available today, what funds are being made available to rapidly test them to improve outcomes in West Africa for patients with Ebola?**

NIAID Response: In the fiscal year 2015 omnibus appropriations legislation, the Congress provided $238 million in emergency funds to NIAID to support research on Ebola vaccines, therapeutics, and diagnostics. This figure includes funds to accelerate the development of therapeutic interventions currently in the product development pipeline. Promising therapeutics will be assessed in preclinical testing including toxicology, *in vitro* testing, and animal model evaluations. Products successful in preclinical testing will be advanced to Phase I clinical trials and, if warranted, further clinical testing in West Africa. It is important to note that the emergency funding for Ebola research also will support clinical testing of Ebola vaccine candidates in West Africa. These Phase II/III clinical studies may be a crucial factor in determining how best to prevent additional cases of Ebola virus disease in the current outbreak and any future outbreaks. Finally, it is important to have additional candidates ready to be

assessed, should current candidates fail to prove safe and effective in clinical testing. The emergency funding for Ebola research will support the discovery and evaluation of additional Ebola vaccine and therapeutic candidates to ensure a robust product development pipeline.

The Honorable Dr. Michael C. Burgess

1. **Please describe how the NIH is communicating with the Department of Defense on research and development of vaccines, therapeutics, and diagnostics.**

NIAID Response: NIAID's longstanding and successful collaborations with the Department of Defense (DOD) are critical to accelerating efforts to develop treatments and vaccines for Ebola virus disease. NIAID is an active participant in the Public Health Emergency Medical Countermeasure Enterprise (PHEMCE), an interagency effort that coordinates federal activities on preparedness against chemical, biological, radiological, and nuclear threats, including Ebola viruses. NIAID coordinates with DOD on Ebola virus vaccines, therapeutics, and diagnostics through the PHEMCE as well as through extensive communication by NIAID and DOD scientific experts. As an active member of the PHEMCE, NIAID participates in multiple teams and committees to ensure coordination of scientific activity with PHEMCE partners, including DOD. These include Integrated Product Teams that coordinate efforts on particular threats such as filoviruses like Ebola and the Portfolio Advisory Committee that aligns Department of Health and Human Services and DOD medical countermeasure development resources.

For example, in partnership with DOD and others, NIAID is working to accelerate the development of medical countermeasures for Ebola virus. NIAID has collaborated with DOD since 2001 on the development of Ebola and Marburg vaccines based on replication-defective adenoviruses, and has conducted Phase I trials in the United States, Europe, and Africa on Ebola vaccines based on the chimpanzee recombinant adenovirus cAd3. NIAID recently expanded the collaboration with DOD to evaluate antiviral therapeutics.

Currently, NIAID and DOD are coordinating to accelerate production of two Ebola vaccine candidates. NIAID and DOD are collaborating with NewLink Genetics on an investigational recombinant vesicular stomatitis virus (VSV)-based vaccine candidate. NIAID and DOD began Phase I safety studies of this VSV vaccine candidate in the fall of 2014 at Walter Reed Army Institute of Research in Silver Spring, Maryland, and at the NIH Clinical Center in Bethesda, Maryland. Another vaccine candidate, the result of a partnership between NIAID researchers, DOD, and Thomas Jefferson University, is based on an Ebola glycoprotein expressed in a recombinant rabies vaccine construct. This rabies-based vaccine candidate provides protection against rabies and Ebola virus disease in a monkey model. In September, NIH licensed the candidate rabies/Ebola vaccine to Exxell BIO of St. Paul, Minnesota, which aims to advance the product through clinical testing and potential commercialization. Clinical lots of the vaccine are currently being manufactured, and Phase I trials are planned for mid-2015.

In addition, NIAID is partnering with DOD and the Biomedical Advanced Research and Development Authority (BARDA) on development of the Ebola therapeutic candidate ZMapp. ZMapp, developed by Mapp Biopharmaceutical, Inc., with support from NIAID and DOD, is a combination of three monoclonal antibodies that can protect monkeys from death due to Ebola virus. NIAID is working closely with partners at DOD, BARDA, and others to help determine whether ZMapp is safe and effective. BARDA is working with Mapp Biopharmaceuticals to accelerate the manufacturing of more ZMapp for further development.

These collaborations with DOD will be critical to advance the development of diagnostics, therapeutics, and vaccines for Ebola viruses. NIAID will continue to play an active role in the PHEMCE and coordinate closely with DOD and other partners to accelerate the development of effective countermeasures for the current Ebola outbreak in West Africa and any future outbreaks.

Congress of the United States
Washington, DC 20515

January 8, 2015

Dr. Luciana Borio
Assistant Commissioner
Counterterrorism Policy
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Dr. Borio:

Thank you for appearing before the Subcommittee on Health on Wednesday, November 19, 2014, to testify at the hearing entitled "Examining Medical Product Development in the Wake of the Ebola Epidemic."

Pursuant to the Rules of the Committee on Energy and Commerce, the hearing record remains open for ten business days to permit Members to submit additional questions for the record, which are attached. The format of your responses to these questions should be as follows: (1) the name of the Member whose question you are addressing, (2) the complete text of the question you are addressing in bold, and (3) your answer to that question in plain text.

Also attached are Member requests made during the hearing. The format of your responses to these requests should follow the same format as your responses to the additional questions for the record.

To facilitate the printing of the hearing record, please respond to these questions and requests with a transmittal letter by the close of business on Thursday, January 22, 2015. Your responses should be mailed to Adrianna Simonelli, Legislative Clerk, Committee on Energy and Commerce, 2125 Rayburn House Office Building, Washington, D.C. 20515 and e-mailed in Word format to **Adrianna.Simonelli@mail.house.gov**.

Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely,

Joseph R. Pitts
Chairman
Subcommittee on Health

cc: The Honorable Frank Pallone, Jr., Ranking Member, Subcommittee on Health

Attachments

Congress of the United States
Washington, DC 20515

January 8, 2015

Rear Admiral Steve Redd
Senior Advisor for Ebola Response
Centers for Disease Control and Prevention
1600 Clifton Road
Atlanta, GA 30333

Dear Admiral Redd:

Thank you for appearing before the Subcommittee on Health on Wednesday, November 19, 2014, to testify at the hearing entitled "Examining Medical Product Development in the Wake of the Ebola Epidemic."

Pursuant to the Rules of the Committee on Energy and Commerce, the hearing record remains open for ten business days to permit Members to submit additional questions for the record, which are attached. The format of your responses to these questions should be as follows: (1) the name of the Member whose question you are addressing, (2) the complete text of the question you are addressing in bold, and (3) your answer to that question in plain text.

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Sincerely,

Joseph R. Pitts
Chairman
Subcommittee on Health

cc: The Honorable Frank Pallone, Jr., Ranking Member, Subcommittee on Health

Attachment

Committee on Energy and Commerce, Subcommittee on Health
"Examining Medical Product Development in the Wake of the Ebola Epidemic"
Testimony of Dr. Steven Redd
Wednesday, November 19 2014
Questions for the Record

NOTE: CONTENT ACCURATE AS OF JANUARY 20, 2015

The Honorable Joseph R. Pitts

1. **As you know, BARDA and CDC need to coordinate efforts as Medical Countermeasures (MCM) products transition from the advanced research and development phase to the approval phase and stockpiling in the Strategic National Stockpile (SNS). I believe BARDA and CDC must a better job working together to avoid any gaps or delays that could be created if the agencies have conflicting stockpile priorities. What steps to you think BARDA and CDC could take to improve coordination of the SNS?**

Response: CDC's Strategic National Stockpile participates in the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) along with BARDA to meet the anticipated medical countermeasure requirements to protect the nation's health security. The collaborative nature of the PHEMCE process ensures that the requirements generated for both BARDA advanced development and SNS procurement are balanced and manageable within projected funding to meet the nation's public health security needs. CDC continues to explore adjustments to the formulary through PHEMCE and the SNS annual review process in combination with a risk-based approach in which additional factors such as adversary capabilities, resources, motivations and preferences as gleaned from the intelligence community are then put together with information on how MCM could be used to mitigate the effects of an attack. Improved understanding of these factors will inform the PHEMCE process and prioritization, shaping the SNS formulary to maximize the surge capability provided by SNS assets within existing funding projections. A document outlining the PHEMCE decision process is attached for supporting reference.

2. **How are you ensuring we are maintaining adequate supplies of approved and purchased medical countermeasures?**

Response: As discussed above, CDC participates in the PHEMCE governance process to ensure that appropriated SNS funding is used to most effectively meet anticipated medical countermeasure requirements. The results of CDC activities to maintain adequate supplies of approved medical countermeasures in the SNS are published annually in the PHEMCE Report on the SNS Annual Review. The most recent version, the 2013 SNS Annual Review Report, was released in August 2014.

As there are no FDA-approved vaccines or licensed medications for Ebola, CDC has and will continue to work to assure that there are adequate supplies of Personal Protective Equipment (PPE) to assure that

healthcare workers providing care for Ebola patients are protected. This effort requires coordination with hospitals, state and local authorities, as well as with domestic and global manufacturers. Following the release of the updated PPE guidance by CDC in late October, CDC began a dedicated effort to increase PPE inventory in the Strategic National Stockpile (SNS) that can be deployed to hospitals if needed to supplement other supply mechanisms. CDC has bolstered the SNS by ordering $2.7 million in PPE supplies. With $8 million in supplemental funding, CDC will procure additional personal protective equipment (PPE) for stockpiling in the Strategic National Stockpile. The PPE procured would equate to a total of approximately 750 days of patient care. In the event that PPE is unavailable from other sources, CDC can deliver supplies to U.S. hospitals caring for Ebola patients. Hospitals should coordinate with their state public health departments if there is a need to request PPE supplies from CDC.

The Honorable Eliot L. Engel

3. **Despite our best efforts, we know the only way to ensure there are no Ebola cases in the United States are to end the outbreak in West Africa. UN Special Envoy on Ebola, Dr. David Nabarro, recently said the extraordinary global response over the past month has made him hopeful outbreak could end in 2015, but he made clear that efforts to contain the disease is not even a quarter done. What are the key components that are still lacking in the international response? How would CDC utilize the proposed funding in the supplemental request to address these needs?**

Response: CDC, in coordination with international and national partners, is committed to getting to zero cases of Ebola in West Africa. While this is not an exhaustive list, it highlights the key interventions that must be continued or scaled up in order to get to zero cases:

- Obtaining the cooperation of communities in working with health workers to promptly report suspect cases and community deaths, encourage them to be placed in ETUs or buried in a safe manner and facilitate contact tracing.
- Mobilizing the needed human resources for case finding and contact tracing at subnational levels.
- Rapid response teams at the national level to investigate suspect cases in areas that have never had or not had recent cases, and logistic support including helicopters for these teams.
- Improvements in IT infrastructure and data collection and management systems to improve information management.
- Enhance coordination of national and international staff to appropriately manage human and material resources.

CDC received Emergency Funding in FY 2015 to support Ebola Response and support National Public Health Institutes and expand the Global Health Security Agenda activities, primarily in Africa. The funding will address the above mentioned priority actions in the three highly affected Ebola countries and will ensure that CDC can support those countries at highest risk for imported cases, to prevent, detect, and respond to infectious disease threats.

4. **Currently the UN is leading their Ebola response from Ghana, but many countries could benefit from having an Ebola readiness and response mechanisms in place to bolster the resilience, technology and infrastructure in the region in order to respond to this and future outbreaks. What has the United States done to aid countries that are directly affected by, and/or adjoining to neighboring countries directly affected by, with response to Ebola and blood safety and preparedness?**

Response: Since mid-2014, CDC has been actively involved in supporting countries directly affected and at risk for Ebola. CDC's activities support efforts to prevent, detect, and respond to the Ebola at home and abroad through the following activities to directly support affected and adjoining countries:

- Provide technical assistance and direct staff support to control the epidemic in the hardest hit countries in Africa by funding and undertaking activities including: infection control, contact tracing and laboratory surveillance and training; emergency operation centers and preparedness; education and outreach.
- Provide technical expertise to high risk unaffected countries to prepare them to respond quickly to potential Ebola cases including in the areas of: contact tracing, emergency operation centers (EOCs), early alert systems, specimen transport to laboratories, rapid response teams and infection control.
- Conduct evaluations of clinical trials in affected countries to assess safety and efficacy of vaccine candidates.
- Establish global health security capacity in vulnerable countries to prevent, detect and respond to outbreaks before they become epidemics by: standing up emergency operations centers; providing equipment and training needed to test patients and report data in real-time; providing safe and secure laboratory capacity; and developing a trained workforce to track and end outbreaks before they become epidemics. These latter activities intended to increase global health security capacity are the same activities that are necessary to combat the spread of Ebola and reduce the potential for future outbreaks of infectious diseases that threaten to become similarly devastating epidemics.

Congress of the United States
Washington, DC 20515

January 8, 2015

Dr. Robin Robinson
Director
Biomedical Advanced Research and Development Authority
Office of the Assistant Secretary for Preparedness and Response
U.S. Department of Health and Human Services
200 Independence Avenue, S.W.
Washington, D.C. 20201

Dear Dr. Robinson:

Thank you for appearing before the Subcommittee on Health on Wednesday, November 19, 2014, to testify at the hearing entitled "Examining Medical Product Development in the Wake of the Ebola Epidemic."

Pursuant to the Rules of the Committee on Energy and Commerce, the hearing record remains open for ten business days to permit Members to submit additional questions for the record, which are attached. The format of your responses to these questions should be as follows: (1) the name of the Member whose question you are addressing, (2) the complete text of the question you are addressing in bold, and (3) your answer to that question in plain text.

To facilitate the printing of the hearing record, please respond to these questions with a transmittal letter by the close of business on Thursday, January 22, 2015. Your responses should be mailed to Adrianna Simonelli, Legislative Clerk, Committee on Energy and Commerce, 2125 Rayburn House Office Building, Washington, D.C. 20515 and e-mailed in Word format to **Adrianna.Simonelli@mail.house.gov**.

Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely,

Joseph R. Pitts
Chairman
Subcommittee on Health

cc: The Honorable Frank Pallone, Jr., Ranking Member, Subcommittee on Health

Attachment

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

The Honorable Joseph R. Pitts
Chairman
Subcommittee on Health
Committee on Energy and Commerce
House of Representatives
Washington, D.C. 20515-6115

FEB 18 2015

Dear Mr. Chairman:

Thank you for providing the Food and Drug Administration (FDA or the Agency) with the opportunity to testify at the November 19, 2014, hearing before the Subcommittee on Health entitled "Examining Medical Product Development in the Wake of the Ebola Epidemic." This is the response for the record to questions posed by several Committee Members, which we received on January 8, 2015.

Please let us know if you have any further questions.

Sincerely,

Thomas A. Kraus
Associate Commissioner for Legislation

cc: The Honorable Frank Pallone, Jr.
Ranking Member
Subcommittee on Health

We have restated each Member's questions below in bold, followed by our responses.

The Honorable Joseph R. Pitts

1. **Given the long time line required to develop new vaccines and therapeutics and then demonstrate clinical safety, what initiatives are underway at the Department of Health and Human Services (HHS) to improve care for patients who are infected with Ebola today?**

BARDA is responding to this question. Please see BARDA QFR 16.

2. **Given many of the well-reported supply challenges with mass-producing and manufacturing Ebola drug treatments, such as ZMapp and others, in the near-term pipeline of Ebola experimental and investigational treatments, do you see potential paths forward that could have the drug supply available to actually treat thousands of Ebola patients in West Africa?**

BARDA is responding to this question. Please see BARDA QFR 17.

3. **What is the role and pathway to join the global coalition of clinical trials for finding effective new experimental therapies in patients with Ebola Virus Disease in West Africa?**

Properly designed and conducted clinical trials are the fastest and most effective way to determine if investigational products for Ebola are safe and effective. FDA strongly favors international collaboration in the design and conduct of clinical trials to ethically generate interpretable data showing whether proposed treatments are safe and effective for patients with Ebola virus disease. FDA welcomes submissions of proposals for and data from such trials for review. The infrastructure to conduct clinical trials in affected West African countries is limited and efforts are underway, including by the U.S. government, to build the infrastructure required for the conduct of critical clinical trials. FDA is providing scientific and technical assistance to the World Health Organization (WHO), which is helping to coordinate international efforts to develop medical products to prevent and treat Ebola virus disease, and is helping affected countries prioritize the investigational products for clinical testing. Medical product sponsors who want to conduct a clinical trial with an investigational product for Ebola in West Africa should work with their local regulatory authority (e.g., FDA or the European Medicines Agency) as well as with WHO and the relevant authorities in the country in which they wish to conduct a trial.

4. **How would a treatment that focused on surviving the deadly complications of Ebola rather than the virus itself be tested in the coalition forming for clinical trials in West Africa?**

Sponsors and developers of products focused on specific complications of Ebola virus disease are welcome to submit proposals for review and feedback for how they would show benefit against such complications.

5. **For experimental treatments that are available today, what funds are being made available to rapidly test them to improve outcomes in patients in West Africa for patients with Ebola?**

BARDA is answering this question. Please see BARDA QFR 20.

The Honorable Marsha Blackburn

1. **How many companies have requested the ability to export investigational new drugs pursuant to the U.S. Food and Drug Administration's ("FDA") investigational new drug emergency export provisions (21 C.F.R. § 312.110 (b)(5))?**

There are several FDA provisions applicable to the export of investigational drugs. Most frequently, drugs are exported under an Investigational New Drug application (IND) for clinical trials, when the sponsor can provide to FDA data that support the ethical study of the drug in humans or are exported under provisions of the law that permit export for investigational use to a country with an advanced regulatory system (21 USC 382(e), 21 CFR 312.110(b)(1) or (3)). Even in situations in which the exporter is seeking to export to a country without an advanced regulatory system, and is unable or chooses not to submit data to FDA to justify human use of its product, FDA regulations permit export based on simple requirements that the drug comply with the laws of the country to which it is being exported, requirements of certification concerning proper manufacture and lack of adulteration, requirements of approval of clinical studies by an independent ethics committee, and requirements that test subjects be afforded informed consent before use of the drug (21 CFR 312.110 (b)(4), 312.120).

The provision found in 21 CFR 312.110(b)(5)(ii) is intended for a sudden and immediate national emergency in a foreign country in which not even the certifications designed to protect patients and test subjects identified under (b)(4) are required. This provision is not an alternative to regulatory review of the product for companies that simply choose not to, or are unable to, make the certifications required by (b)(4). Instead, it is a rarely used provision that would be expected to be applied only in those circumstances in which there was an established basis for use of the investigational drug but there was not time to utilize the usual processes for export. This provision requires a determination by the Secretary of Health and Human Services, or her designee, that prompt export is necessary, based on information provided by an authorized official of the importing country's government.

This provision has been used in one circumstance, making available to health care workers in Liberia afflicted with Ebola the few available doses of a drug with reported activity against Ebola in animal models and that had been provided to persons with the Ebola virus in the United States under an expanded access individual IND. One other request to use this provision for export of a different drug did not result in a Secretarial determination because the public health authorities of the country of intended export withdrew the request.

2. **When were those requests received by the Department of Health and Human Services ("DHHS")?**

One request under 312.110(b)(5) was received August 8, 2014, and the other, October 24, 2014.

3. When were those same requests forwarded to the FDA for advice and consultation?

Any requests received by HHS under 312.110(b)(5) have been forwarded to FDA within the same day of receipt.

4. If any of those requests have been supported by DHHS to date, when was the respective company notified?

For the request meeting the requirements of 312.110(b)(5)(ii), the requesting country and respective company were notified on August 11, 2014.

5. Please explain the nature of DHHS's consultations with FDA. Which divisions of DHHS and FDA have primary authority in such consultations?

HHS and FDA are in daily communications about Ebola response efforts. Communications about export requests occur within the Ebola Response working group structures and at leadership levels.

6. If DHHS or FDA needs more information in order to complete their consultation, will they consult with the respective company?

If more information is needed from the respective company, FDA will request such information.

7. Have any countries made requests [to] import investigation[al] new drugs pursuant to FDA's investigations new drug emergency export provisions? If so, have they been notified of the timeline for consideration of their request?

The U.S. government is working with the international community, including the affected countries' ministries of health, and companies that have submitted data to FDA that show some promise of effectiveness to facilitate clinical trials in affected countries, for the best candidates available. FDA has received and granted one request under 21 CFR 312.110(b)(5)(ii). In one circumstance, HHS received a request from an official not otherwise engaged in the international response efforts. HHS and FDA responded promptly to address this request through appropriate government and diplomatic communication channels. The request was ultimately withdrawn.

The Honorable Michael C. Burgess

1. As the FDA fails to consider all options when it comes to vaccine, diagnostic, and drug development, how will you assess studies performed outside of the United States *not* under FDA's guidance if they prove to be safe and efficacious?

Product sponsors and developers should submit all relevant data to FDA concerning their products, when they seek development advice and/or approval for U.S. marketing. Criteria

for accepting foreign clinical studies not conducted under an IND are outlined in 21 CFR 312.120 and focus on ensuring ethical conduct and scientific quality of the trials.

2. **How are you evaluating the risk profile of therapeutics given the high mortality rate from Ebola?**

FDA review takes into account the balance between risks and benefits for the populations in which use of a product is anticipated. This includes recognizing that greater risks of adverse events may be considered acceptable if a product shows substantial benefit in treatment of a serious life-threatening condition without other treatment options, than for a product that is likely to be given to persons with minor self-limiting illness or to healthy persons at low risk of illness.

3. **How are you ensuring that you are prioritizing the right, and the most promising, vaccines, therapeutics, and diagnostics?**

FDA is providing scientific and regulatory advice to U.S. government agencies that are supporting medical product development for Ebola and product sponsors to clarify regulatory requirements, review and provide input on pre-clinical and clinical trial designs, and expedite the regulatory review of data as they are received from product developers. Facilitating the development and availability of investigational medical products for Ebola is a high priority for FDA, and the Agency reviews all proposals and data from product sponsors and developers based on the information available for each. We give high priority to supporting the U.S. government pipeline of investigational medical products for Ebola, which is prioritized through a well-established, inter-agency process to identify and support the most promising candidates.

4. **Currently, there are six rapid diagnostics that have been approved for Emergency Use Authorization. What is the plan for providing a pathway to approval for these diagnostics when the Ebola crisis winds down?**

FDA issued a seventh Emergency Use Authorization (EUA) on December 23, 2014. FDA encourages and expects sponsor/applicants who have received an EUA for their diagnostic device to pursue clearance or approval of their device at a later date. If an authorization has been in effect for more than a year, FDA is required to provide an explanation of the scientific, regulatory, or other obstacles to the approval of the product. FDA will work closely with these device sponsors/applicants and will identify in writing any potential obstacles to approval and actions to be taken by FDA and sponsors/applicants to overcome them.

5. **False negatives are a real concern in testing for Ebola. In the case of the physician from Maryland who was treating patients in Sierra Leone, treatment was delayed because of a false negative on his initial Ebola test. How are you combatting confounding false negatives?**

As part of the EUA process, FDA reviews the totality of scientific evidence, including data on the device performance, before it can determine that the product may be effective in diagnosing Ebola infections and can conclude that the known and potential benefits of the

product outweigh the known and potential risks. To date, FDA has not received reports of false-negative results obtained with an FDA authorized Ebola test. However, it should be noted that no diagnostic test is 100 percent accurate, and there are factors such as quality and timing of specimen collection that will influence test results.

6. How is the efficacy of the tests receiving Emergency Use Authorization being tested?

There are two types of diagnostic tests being developed for Ebola; molecular and serologic. Molecular tests analyze variations in the sequence, structure, or expression of genetic material (i.e., deoxyribonucleic acid (DNA) and ribonucleic acid (RNA)) in order to diagnose a disease or medical conditions. Serologic tests detect antibodies and antigens specific to an identifiable pathogen in order to diagnose a disease or medical conditions.

Typically, molecular Ebola diagnostics receiving EUA undergo the following testing:

- Limit of Detection (LoD) - This study determines the lowest detectable concentration of Ebola Virus at which at least 95 percent of all replicates test positive. The LoD is determined by limiting dilutions of titered or otherwise quantified Ebola virus materials in a relevant clinical matrix.
- Reactivity - These studies show whether the device can detect multiple strains of Ebola virus at concentrations near the limit of detection.
- Cross Reactivity -These studies test the assay's ability to exclusively identify Ebola virus with no cross-reactivity to other organisms that might be present in the relevant clinical specimen types and can cause symptoms similar to those observed at the onset of an Ebola infection, and
- Mock Clinical Evaluation - The performance characteristics of this test are established using contrived specimens (individual negative clinical specimens spiked with different dilutions of Ebola virus material) when positive clinical specimens are not available.

Testing for serologic Ebola diagnostics include:

- Limit of Detection (LoD),
- Reactivity
- Cross -reactivity
- Interfering substances that may have the ability to generate false-positive and false-negative results
- High-Dose Hook Effect –refers to the false-negative result, which can be seen when very high levels of target are present in a tested sample, and
- Mock Clinical Evaluation - The performance characteristics of this test are established using contrived specimens (individual negative clinical specimens spiked with different dilutions of Ebola virus material), when positive clinical specimens are not available.

The Honorable Eliot L. Engel

1. **I have frequently said that the U.S. cannot meet the challenge that Ebola presents alone. Ebola is a global challenge requiring a global response. Can you discuss how the FDA is working with our international partners to facilitate collaboration and the exchange of important information on investigational products for Ebola?**

FDA is collaborating with the World Health Organization (WHO) and international regulatory counterparts to exchange information about investigational products for Ebola in support of international response efforts and to achieve regulatory harmonization, when possible. These collaborations are supported by confidentiality commitments, when necessary, to enable the sharing of non-public information. FDA international collaborations include:

- Participating in a WHO consultation to develop guidance on the ethical considerations for use of investigational interventions for Ebola
- Providing technical assistance to WHO on the development of convalescent whole blood or plasma for the treatment of Ebola
- Participating in several WHO consultations to discuss leading investigational treatments and vaccines for Ebola and key considerations for clinical testing and deployment
- Participating in a WHO-sponsored regulatory working group of international health regulators
- Participating in the WHO Scientific and Technical Advisory Committee for Ebola Experimental Interventions to help facilitate and accelerate appropriate clinical testing of investigational products for Ebola
- Participating in numerous engagements with our international regulatory counterparts — including the European Medicines Agency, Medicines and Healthcare Products Regulatory Agency (UK), Paul-Ehrlich-Institut (Germany), Health Canada, and others — to exchange information on investigational products for Ebola.

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